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=> d his

     (FILE 'HOME' ENTERED AT 20:11:00 ON 24 OCT 2003)

     FILE 'REGISTRY' ENTERED AT 20:11:08 ON 24 OCT 2003
                E GABAPENTIN/CN
L1            2 S E3-E4

     FILE 'HCAPLUS, USPATFULL' ENTERED AT 20:12:18 ON 24 OCT 2003
L2           97 S L1 AND SALT? AND (HYDROCHLORIC OR HYDROBROMIC? OR HYDROIODIC?
L3           97 DUP REM L2 (0 DUPLICATES REMOVED)
L4            9 S L3 AND PPM
L5           83 S L1 AND SALT? AND (HYDROBROMIC? OR HYDROIODIC? OR PHOSPHORIC?
L6           83 DUP REM L5 (0 DUPLICATES REMOVED)
L7            2 S L6 AND PPM
L8            7 S L4 NOT L7

     FILE 'STNGUIDE' ENTERED AT 20:22:47 ON 24 OCT 2003
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FILE 'HCAPLUS' ENTERED AT 20:12:18 ON 24 OCT 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'USPATFULL' ENTERED AT 20:12:18 ON 24 OCT 2003
CA INDEXING COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

=> d his

     (FILE 'HOME' ENTERED AT 20:11:00 ON 24 OCT 2003)

     FILE 'REGISTRY' ENTERED AT 20:11:08 ON 24 OCT 2003
               E GABAPENTIN/CN
L1            2 S E3-E4

     FILE 'HCAPLUS, USPATFULL' ENTERED AT 20:12:18 ON 24 OCT 2003

=> s l1 and salt? and (hydrochloric or hydrobromic? or hydroiodic? or phosphoric?
or nitric? or sulfuric? or sulphuric? or sulfonic? or sulphonic? or
methanesulfonic? or methanesulphonic?)(3a)acid?
L2           97 L1 AND SALT? AND (HYDROCHLORIC OR HYDROBROMIC? OR HYDROIODIC?
                OR PHOSPHORIC? OR NITRIC? OR SULFURIC? OR SULPHURIC? OR SULFONIC
                ? OR SULPHONIC? OR METHANESULFONIC? OR METHANESULPHONIC?)(3A)
                ACID?

=> dup rem l2
PROCESSING COMPLETED FOR L2
L3            97 DUP REM L2 (0 DUPLICATES REMOVED)

=> s l3 and ppm
L4             9 L3 AND PPM

=> d l4 abs ibib kwic hitstr 1-9

L4   ANSWER 1 OF 9  USPATFULL on STN
AB     Stable compositions containing gabapentin compositions, methods of
       preparing such compositions, and methods of using such compositions.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER:        2003:174060  USPATFULL
TITLE:                   Stable gabapentin compositions
INVENTOR(S):             Cannata, Vincenzo, Sasso Marconi, ITALY
                         Corcella, Francesco, Rozzano, ITALY
                         Nicoli, Andrea, Vicenza, ITALY
PATENT ASSIGNEE(S):      ZAMBON GROUP S.P.A., Milan, ITALY, 20091 (non-U.S.
                         corporation)

                              NUMBER        KIND    DATE
                         ---------------- ------ --------
PATENT INFORMATION:      US 20031199088      A1   20030626
APPLICATION INFO.:       US 2001-24339       A1   20011221  (10)
DOCUMENT TYPE:           Utility
FILE SEGMENT:            APPLICATION
LEGAL REPRESENTATIVE:    OBLON, SPIVAK, MCCLELLAND, MAIER & NEUSTADT, P.C., 1940
                         DUKE STREET, ALEXANDRIA, VA, 22314
NUMBER OF CLAIMS:        73
```

EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Page(s)
LINE COUNT: 485
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . describes a method of preparing gabapentin which is free of the gabapentin lactam. These gabapentin compositions contain less than 20 **ppm** of an anion of a mineral acid

SUMM [0008] It is another object of the present invention to provide compositions containing more than 20 **ppm** of an anion of a mineral acid, e.g., chloride.

SUMM . . . Accordingly, the objects of the invention, and others, may be accomplished with a composition comprising gabapentin and at most 5 **ppm**, based on the amount of the gabapentin, of an addition **salt** of gabapentin and an acid.

SUMM [0014] (b) at most 5 **ppm**, based on the amount of the gabapentin, of an addition **salt** of gabapentin and an acid; and

SUMM [0018] (b) at least one **salt** of a nonacidic cation and an anion of a mineral acid, and

SUMM [0020] wherein the composition contains at least 20 **ppm** of the anion of a mineral acid, based on the amount of the gabapentin.

DETD . . . synthesized via the Hofmann rearrangement described in U.S. Pat. No. 4,024,175. Such a process produces a solution of the hydrochloride **salt** of gabapentin. This material may then be extracted or crystallized to produce a gabapentin solution containing 5 and 10 molar. . .

DETD [0030] Content of Acid Addition **Salt** of Gabapentin

DETD [0031] In one embodiment, the composition of the present invention contains gabapentin and at most 5 **ppm**, based on the amount of the gabapentin, of an acid addition **salt** of gabapentin and an acid (hereinafter referred to as "the acid addition **salt**").

DETD [0032] The most relevant acid addition **salt** is gabapentin hydrochloride, i.e., the **salt** of gabapentin and **hydrochloric acid**. However, the **acid** may be another mineral **acid** such as **hydrobromic acid**, **hydroiodic acid**, **phosphoric acid**, **nitric acid**, **sulfuric acid**, **sulfonic acid**, or **methanesulfonic acid**.

DETD [0033] The amount of the acid addition **salt** may be lower than 5 **ppm**, such as 4, 3, 2, 1, 0.5, 0.25, 0.1, 0.05 **ppm** or less.

DETD [0034] It is particularly preferred that the composition contains an undetectable amount of the addition **salt** of **hydrochloric acid** in a silver nitrate titration assay. This assay may be performed by potentiometrically titrating with 0.01 N aqueous silver nitrate. . . a solution obtained by dissolving 7.5 grams of the composition in 100 mL of methanol/water (80/20 by volume) followed by **acidification** with **nitric acid**. This assay is well-known to those skilled in the art.

DETD [0035] **Salt** of an Nonacidic Cation and an Anion of a Mineral Acid

DETD [0036] In another embodiment, the composition of the present invention gabapentin and at least one **salt** of a nonacidic cation and an anion of a mineral acid, wherein the composition comprises more than 20 **ppm** of the anion of a mineral acid, based on the amount of the gabapentin. As used herein, the term "nonacidic. . . a Bronsted or a Lewis acid. Thus, the amount of the anion of the mineral acid is higher than 20 **ppm**, such as 25, 30, 40, 50, 75, 100, 250, 500, 1000,

2000, 2500, 3000 **ppm**, or more.

DETD [0037] Such a composition may be prepared, for example, by adding one or more **salts** of of a nonacidic cation and an anion of a mineral acid to the gabapentin produced with less than 5 **ppm** of the acid addition **salt** as described above.

DETD [0038] The composition may also be prepared by adding the appropriate amount of the nonacidic cation hydroxide **salt** (e.g., NaOH) to a sample of gabapentin containing more than 20 **ppm** of chlorides in order to transform the existing chlorides into a **salt** with the nonacidic cation (e.g., NaCl).

DETD [0039] In one embodiment, the composition additionally comprises at most 5 **ppm** of one or more addition **salts** of gabapentin and an acid. The amount of the acid addition **salt** may be lower than 5 **ppm**, such as 4, 3, 2, 1, 0.5, 0.25, 0.1, 0.05 **ppm** or less.

DETD [0043] A preferred anion is chloride. A particularly preferred **salt** is sodium chloride.

DETD [0063] The stbility of a gabapentin compositions containing 60, 70, or 80 **ppm** of gabapentin hydrochloride (GABA-HCl) was measured at 40.degree. C. by HPLC over a period of 3 months. The total amount. . .

DETD [0064] The stbility of a gabapentin compositions which was chloride free, i.e., no GABA-HCl, contained 70 **ppm** of NH.sub.4Cl or 70 **ppm** of GABA-HCl was measured at 40.degree. C. by HPLC over a period of 3 months. The total amount of impurities. . .

DETD . . . The stability of gabapnetin compositions, with respect to gabapentin lactam formation, at 40.degree. C. containing (1) no additives (free of **salts**; denoted reference), (2) 87 **ppm** of NaBr, (3) 50 **ppm** of KCl, (4) 50 **ppm** of Na.sub.2SO.sub.4, (5) 2350 **ppm** of NaCl, (6) 114 **ppm** of HBr, (7) 7 **ppm** of GABA-HCl, or (8) 100 **ppm** of H.sub.2SO.sub.4. The amount of gabapentin lactam produced over 1.5 months was deteremined. The results are shown in FIG. 3. The results of this experiment demonstrated that gabapentin compositions containing a **salt** of a nonacidic cation were quite stable.

DETD [0066] In order to prepare a composition of gabapentin containing 60 **ppm** of chloride (as NaCl), gabapentin (dry, 330 g), demineralized water (165 g), and methanol (218 g) were charged into a. . . resulting solid was then filtered and washed on the filter with 330 g of a NaCl solution in isopropanol/water (308 **ppm**). The product was then dried in an oven at 50.degree. C. for 17 hours. As a result, gabapentin (307.5 g) was obtained with a chloride content of 60 **ppm** as measured by potentiometric titration with AgNO.sub.3. Gabapentin containing different amounts of chloride (as NaCl), e.g., 70 or 80 **ppm**, can be prepared in a similar fashion.

DETD [0067] In order measure the stability of such compostions, samples prepared as described above containing (1) 60 **ppm** of chloride as NaCl, (2) 80 **ppm** of chloride as NaCl, and (3) 60 **ppm** of chloride as NaCl (duplicate) were stored at 40 C and anlyzed by HPLC to determine the amount of degredation. . .

DETD . . . teaches that the content of an anion of a mineral acid in a gabapentin composition must be less than 20 **ppm**. This experiment demonstrates that no meaningful degredation occurs and the amount of gabapentin lactam remains close to zero.

CLM What is claimed is:

1. A composition comprising gabapentin and at most 5 **ppm**, based on the amount of the gabapentin, of an addition **salt** of gabapentin and an acid.

2. The composition of claim 1, comprising at most 4 **ppm** of the addition **salt** of gabapentin and an acid.

3. The composition of claim 1, comprising at most 3 **ppm** of the addition **salt** of gabapentin and an acid.

4. The composition of claim 1, comprising at most 2 **ppm** of the addition **salt** of gabapentin and an acid.

5. The composition of claim 1, comprising at most 1 **ppm** of the addition **salt** of gabapentin and an acid.

6. The composition of claim 1, comprising at most 0.5 **ppm** of the addition **salt** of gabapentin and an acid.

7. The composition of claim 1, comprising at most 0.25 **ppm** of the addition **salt** of gabapentin and an acid.

8. The composition of claim 1, comprising at most 0.1 **ppm** of the addition **salt** of gabapentin and an acid.

9. The composition of claim 1, comprising at most 0.05 **ppm** of the addition **salt** of gabapentin and an acid.

10. The composition of claim 1, comprising no detectable quantity of the addition **salt** of gabapentin and an acid.

11. The composition of claim 9, which contains no detectable quantity of the addition **salt** of gabapentin by silver nitrate titration.

13. The composition of claim 1, wherein the mineral acid is selected from the group consisting of **hydrochloric acid**, **hydrobromic acid**, **hydroiodic acid**, **phosphoric acid**, **nitric acid**, **sulfuric acid**, **sulfonic acid**, **methanesulfonic acid**.

14. The composition of claim 1, wherein the mineral **acid** is **hydrochloric acid**.

18. A pharmaceutical composition in dry unit dosage form, comprising: (a) gabapentin; (b) at most 5 **ppm**, based on the amount of the gabapentin, of an addition **salt** of gabapentin and an acid; and (c) at least one nonacidic pharmaceutically acceptable excipient.

19. A composition, comprising gabapentin and at least one **salt** of a nonacidic cation and an anion of a mineral acid, wherein the composition comprises more than 20 **ppm** of the anion of a mineral acid, based on the amount of the gabapentin.

20. The composition of claim 19, which contains more than 25 **ppm** of the anion of a mineral acid, based on the amount of the gabapentin.

21. The composition of claim 19, which contains more than 30 **ppm** of the anion of a mineral acid, based on the amount of the gabapentin.

22. The composition of claim 19, which contains more than 50 **ppm** of the anion of a mineral acid, based on the amount of the gabapentin.

23. The composition of claim 19, which contains more than 75 **ppm** of the anion of a mineral acid, based on the amount of the gabapentin.

24. The composition of claim 19, which contains more than 100 **ppm** of the anion of a mineral acid, based on the amount of the gabapentin.

25. The composition of claim 19, which contains more than 250 **ppm** of the anion of a mineral acid, based on the amount of the gabapentin.

26. The composition of claim 19, which contains more than 500 **ppm** of the anion of a mineral acid, based on the amount of the gabapentin.

27. The composition of claim 19, which contains more than 1000 **ppm** of the anion of a mineral acid, based on the amount of the gabapentin.

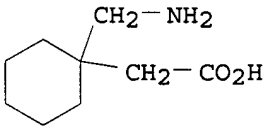
28. The composition of claim 19, which contains more than 2000 **ppm** of the anion of a mineral acid, based on the amount of the gabapentin.

29. The composition of claim 19, comprising at most 5 **ppm** of one or more addition **salts** of gabapentin and an acid.

36. The composition of claim 19, wherein the **salt** is sodium chloride.

37. A pharmaceutical composition in dry unit dosage form, comprising: (a) gabapentin; (b) at least one **salt** of a nonacidic cation and an anion of a mineral acid, and (c) at least one nonacidic excipient wherein the composition contains at least 20 **ppm** of the anion of a mineral acid, based on the amount of the gabapentin.

IT 7647-14-5, Sodium chloride, biological studies **60142-96-3**, Gabapentin
(stable gabapentin compns.)
IT **60142-96-3**, Gabapentin
(stable gabapentin compns.)
RN 60142-96-3 USPATFULL
CN Cyclohexaneacetic acid, 1-(aminomethyl)- (9CI) (CA INDEX NAME)



L4 ANSWER 2 OF 9 USPATFULL on STN
AB A pharmaceutical composition containing substantially pure and stable gabapentin are disclosed wherein gabapentin has a pH of between 6.8 to 7.3.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2003:79181 USPATFULL
TITLE:	Stable gabapentin having pH within a controlled range
INVENTOR(S):	Singer, Claude, Kfar Saba, ISRAEL Pilarski, Gideon, Holon, IL, UNITED STATES Pesachovich, Michael, Givat Shmuel, ISRAEL

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003055109	A1	20030320
APPLICATION INFO.:	US 2002-227244	A1	20020826 (10)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 2001-880922, filed on 15 Jun 2001, ABANDONED		

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-211966P	20000616 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	KENYON & KENYON, 1500 K STREET, N.W., SUITE 700, WASHINGTON, DC, 20005
NUMBER OF CLAIMS:	5
EXEMPLARY CLAIM:	1
LINE COUNT:	619

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . or less of corresponding lactam, (ii) not allowing the anion of a mineral acid in the composition to exceed 20 **ppm**, and (iii) using a specifically selected adjuvant that is not adverse to gabapentin stability.

SUMM . . . It has now been found that Augart's reliance on maintaining the anion of a mineral acid as not exceeding 20 **ppm** is misplaced. Thus, gabapentin and pharmaceutical formulations of gabapentin can be prepared and stored such that initially they do not. . .

SUMM [0010] The specific mineral acid disclosed by Augert is **hydrochloric acid** (column 3, lines 61-63; column 5, lines 24-29; exampes 1 and 2). The specification states, in particular

SUMM . . . for example, from the corresponding hydrochloride by ion exchange. The proportion of remaining hydrochloride admixtures should thereby not exceed 20 **ppm**.

SUMM [0013] 20 **ppm** of gabapentin hydrochloride corresponds to roughly 3 **ppm** of chloride ion, due to the higher molecular weight of gabapentin.

SUMM [0014] Augert's claims require gabapentin with "less than 20 **ppm** of the anion of a mineral acid", e.g. chloride.

SUMM [0018] As will be illustrated through exemplary embodiments 1-16, gabapentin may be prepared from the hydrochloride **salt** of gabapentin (gabapentin hydrochloride) and that in purified form gabapentin may have a pH in the range of 6.8-7.3, and preferably in the range of 7.0-7.2. The gabapentin formulation may also contain more than 20 **ppm** of chloride ion in the composition as measured by the amount of chloride ion in the composition.

SUMM . . . Exemplary embodiments 17-19 illustrate formulations of gabapentin containing varying amounts of chloride ion, some of which are greater than 20 **ppm** and some less, and all of which initially contain less than 0.5% of lactam and after one year of storage. . .

DETD . . . chlorine anion content of the above-prepared gabapentin were obtained:

TABLE 1

Anion content and pH values
after the reslurry in methanol

Run	Cl (ppm)	pH
A	4	6.94
B	20	7.01
C	<5	7.04
D	40	6.97
E	35	6.92
F	15	6.84

DETD . . . under vacuum resulting in pure gabapentin with a yield of 87%, pH of 7.15 and chlorine anion content of 50 ppm. Gabapentin so prepared initially contained less than 0.5% by weight of lactam, and, after a year of storage at 25.degree.. . .

DETD . . . under vacuum, resulting in pure gabapentin having a yield of 85%, pH of 6.8, and chlorine anion content of 50 ppm. Gabapentin so prepared contained less than 0.5% by weight of lactam, and, after a year of storage at 25.degree. C.. . .

DETD . . . reslurry as in Example 1B gabapentin pure was obtained at a yield of 58.8% and chloride anion content of 7 ppm Cl.sup.-.

DETD . . . reslurry as in Example 1B, gabapentin pure was obtained having a yield of 75.0% and chloride anion content of 213 ppm.

DETD . . . process, as in Example 1B, gabapentin pure was obtained having a yield of 68.0% and chloride anion content of 142 ppm.

DETD . . . After reslurry as in Example 1B, gabapentin pure was obtained having a yield of 67.8%, and anion content of 142 ppm.

DETD . . . After reslurry as in Example 1B, gabapentin pure was obtained, having a yield of 57.9%, and anion content of 142 ppm.

DETD . . . reslurry as in Example 1B, gabapentin pure was obtained having a yield of 57.9% and an anion content of 142 ppm.

DETD . . . values were obtained and tabulated in TABLE 2 as follows:

TABLE 2

Anion content and pH values for
crystallization in methanol

Run	Cl (ppm)	pH
A	4	6.94
B	<5	7.2
C	150-200	6.9

DETD . . . under vacuum to give gabapentin pure having a yield of 81.4%, pH of 7.25 and chlorine anion content of 35 ppm.

DETD . . . under vacuum to give gabapentin pure at a yield of 81.4%, pH of 7.08 and anion content of Cl.sup.- 20 ppm.

DETD . . . under vacuum to give gabapentin pure having a yield of 72.4%, pH of 7.28 and anion (Cl.sup.-) content of 20 ppm.

DETD . . . under vacuum to give gabapentin pure having a yield of 75.8%, pH of 7.03 and anion content of (Cl.sup.-) 20 ppm.

DETD . . . under vacuum to give gabapentin pure having a yield of 77.6%, pH of 7.22 and anion (Cl.sup.-) content of 20 ppm.

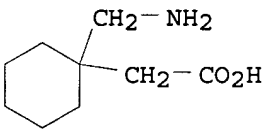
DETD . . . vacuum to give gabapentin pure having a yield of 75%, pH of 7.17 and anion content (Cl.sup.-) of 10 ppm.

DETD [0072] The following gabapentin tablet formulation is prepared using gabapentin containing chloride ion ranging from 5 to 40 ppm and pH in the range of 6.84-7.04 according to Example 1. The following

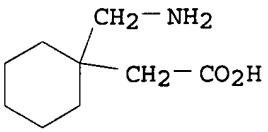
material is used:

Ingredients Amounts

. . .
DETD [0076] Gabapentin of Example 2 (having chloride ion content of 50 **ppm** and pH of 7.15) is used to formulate tablets as in EXAMPLE 17, except that corn starch is replaced in. . .
DETD . . . gabapentin tablet of each sample is initially measured to have 0.5% by weight of a corresponding lactam, more than 50 **ppm** of chloride anion, and pH exceeding 6.8. The tablet is stored for one year at 25.degree. C. and 60% atmospheric. . .
DETD [0078] EXAMPLE 18 is repeated except that gabapentin of Example 4, having chloride ion of 7 **ppm** is used for formulating tablets. The resulting gabapentin tablet of each sample is initially measured to have 0.5% by weight of lactam and approximately 7 **ppm** of chloride anion. The tablet is stored for one year at 25.degree. C. and 60% atmospheric humidity and the increase. . .
DETD . . . show that, contrary to Augart's disclosure, the presence of anion of a mineral acid in an amount greater than 20 **ppm** does not adversely affect the stability of gabapentin when stored for one year at 5 25.degree. C. and 60% humidity. . .
CLM What is claimed is:
5. Gabapentin which contains less than 0.5% of the corresponding lactam, and less than 100 **ppm** of the anion of a mineral acid, which has a pH between 6.8 and 7.3, and which, after one year. . .
IT **60142-96-3P**, Gabapentin
(stable gabapentin having pH within a controlled range)
IT **60142-95-2**, Gabapentin hydrochloride
(stable gabapentin having pH within a controlled range)
IT **60142-96-3P**, Gabapentin
(stable gabapentin having pH within a controlled range)
RN 60142-96-3 USPATFULL
CN Cyclohexaneacetic acid, 1-(aminomethyl)- (9CI) (CA INDEX NAME)



IT **60142-95-2**, Gabapentin hydrochloride
(stable gabapentin having pH within a controlled range)
RN 60142-95-2 USPATFULL
CN Cyclohexaneacetic acid, 1-(aminomethyl)-, hydrochloride (9CI) (CA INDEX NAME)



● HCl

L4 ANSWER 3 OF 9 USPATFULL on STN

AB A process for the preparation of gabapentin of formula (I) ##STR1##

which comprises:

a) reduction of (1-nitromethyl-cyclohexyl)acetonitrile of formula (II) ##STR2##

to give 3-imino-2-aza-spiro[4.5]decan-2-ol of formula (III) ##STR3##

b) transformation of compound (III), by alkali treatment, into 2-hydroxy-2-aza-spiro[4.5]decan-3-one of formula (IV) ##STR4##

c) reduction of compound (IV) to give 2-aza-spiro[4.5]decan-3-one of ##STR5##

d) hydrolysis of compound (V) to gabapentin.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2003:11350 USPATFULL		
TITLE:	PROCESS FOR THE PREPARATION OF 1-AMINOMETHYL-1-CYCLOHEXANEACETIC ACID		
INVENTOR(S):	Velardi, Francesco, Cameri, ITALY Fornaroli, Mirco, Cameri, ITALY		
PATENT ASSIGNEE(S):	PROCOS S.P.A, CAMERI, ITALY (non-U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003009055	A1	20030109
	US 6521788	B2	20030218
APPLICATION INFO.:	US 2002-156059	A1	20020529 (10)
	NUMBER		DATE
PRIORITY INFORMATION:	IT 2001-MI2001001132		20010529
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	YOUNG & THOMPSON, 745 SOUTH 23RD STREET 2ND FLOOR, ARLINGTON, VA, 22202		
NUMBER OF CLAIMS:	7		
EXEMPLARY CLAIM:	1		
LINE COUNT:	233		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0004] Said patents disclose the hydrate hydrochloride **salt**, while gabapentin hydrate sodium **salt** is disclosed in U.S. Pat. No. 4,894,476.

SUMM . . . gabapentin ester and of the corresponding lactam (2-aza-spiro[4.5]decan-3-one), the acid hydrolysis of the latter and the treatment of the gabapentin **salt** with ion exchange resins.

DETD . . . is heated at 95.degree. C. for 10 hours, then cooled with ice-water and dropwise added with 43 ml of 30% **hydrochloric acid**. The mixture is stirred for 10' and added with 145 ml of water (exothermic reaction) and 110 ml of isopropyl. . .

DETD [0032] Proton spectrum in CD.sub.3OD (chemical shifts are expressed in **ppm** with tetramethylsilane as internal reference)

Chemical shifts	Multiplicity	Integration	Assignment
1.5-1.6	m	10 H	Cyclohexyl methylenes
2.23	s	2 H	methylene
3.4	s. . .		

DETD . . . g of water are refluxed for 1 hour, then cooled with stirring to precipitate a solid. 105 ml of conc. **hydrochloric acid** are dropped therein without exceeding 30.degree. C., checking pH which should be 1 or lower at the end of the. . .

DETD [0041] Proton spectrum in CD.sub.3OD (chemical shifts are expressed in **ppm** with tetramethylsilane as internal reference)

Chemical shifts	Multiplicity	Integration	Assignment
1.3-1.7	m	10 H	Cyclohexyl methylenes
2.55	s	2 H	methylene
3.55	s. . .		

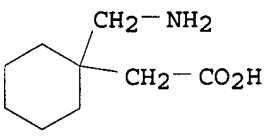
DETD [0047] 2 g (13 mmoles) of compound (V), 10 ml of water and 10 ml of conc. **hydrochloric acid** are refluxed for 4 hours. The mixture is cooled and washed twice with methylene chloride (10 ml each). The combined. . .

IT **60142-95-2P**, Gabapentin hydrochloride **60142-96-3P**, Gabapentin
(process for prepn. of gabapentin)

IT **60142-95-2P**, Gabapentin hydrochloride **60142-96-3P**, Gabapentin
(process for prepn. of gabapentin)

RN 60142-95-2 USPATFULL

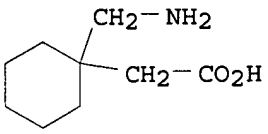
CN Cyclohexaneacetic acid, 1-(aminomethyl)-, hydrochloride (9CI) (CA INDEX NAME)



⊛ HCl

RN 60142-96-3 USPATFULL

CN Cyclohexaneacetic acid, 1-(aminomethyl)- (9CI) (CA INDEX NAME)



L4 ANSWER 4 OF 9 USPATFULL on STN

AB A composition comprising a polypeptide and an active agent covalently attached to the polypeptide. Also provided is a method for delivery of an active agent to a patient comprising administering to the patient a composition comprising a polypeptide and an active agent covalently attached to the polypeptide. Also provided is a method for protecting an active agent from degradation comprising covalently attaching the active agent to a polypeptide. Also provided is a method for controlling release of an active agent from a composition comprising covalently attaching the active agent to the polypeptide.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2002:186092 USPATFULL

TITLE: Active agent delivery systems and methods for protecting and administering active agents

INVENTOR(S): Piccariello, Thomas, Blacksburg, VA, UNITED STATES
Olon, Lawrence P., Bristol, TN, UNITED STATES
Kirk, Randal J., Radford, VA, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002099013	A1	20020725	
APPLICATION INFO.:	US 2001-933708	A1	20010822	(9)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2001-274622P	20010308	(60)
	US 2000-247621P	20001114	(60)
	US 2000-247620P	20001114	(60)
	US 2000-247595P	20001114	(60)
	US 2000-247594P	20001114	(60)
	US 2000-247635P	20001114	(60)
	US 2000-247634P	20001114	(60)
	US 2000-247606P	20001114	(60)
	US 2000-247607P	20001114	(60)
	US 2000-247608P	20001114	(60)
	US 2000-247609P	20001114	(60)
	US 2000-247610P	20001114	(60)
	US 2000-247611P	20001114	(60)
	US 2000-247702P	20001114	(60)
	US 2000-247701P	20001114	(60)
	US 2000-247700P	20001114	(60)
	US 2000-247699P	20001114	(60)
	US 2000-247698P	20001114	(60)
	US 2000-247807P	20001114	(60)
	US 2000-247833P	20001114	(60)
	US 2000-247832P	20001114	(60)
	US 2000-247927P	20001114	(60)
	US 2000-247926P	20001114	(60)

	US 2000-247930P	20001114 (60)
	US 2000-247929P	20001114 (60)
	US 2000-247928P	20001114 (60)
	US 2000-247797P	20001114 (60)
	US 2000-247805P	20001114 (60)
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	US 2000-247803P	20001114 (60)
	US 2000-247802P	20001114 (60)
	US 2000-247801P	20001114 (60)
	US 2000-247800P	20001114 (60)
	US 2000-247799P	20001114 (60)
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	US 2000-247561P	20001114 (60)
	US 2000-247560P	20001114 (60)
	US 2000-247559P	20001114 (60)
	US 2000-247558P	20001114 (60)
	US 2000-247556P	20001114 (60)
	US 2000-247612P	20001114 (60)
	US 2000-247613P	20001114 (60)
	US 2000-247614P	20001114 (60)
	US 2000-247615P	20001114 (60)
	US 2000-247616P	20001114 (60)
	US 2000-247617P	20001114 (60)
	US 2000-247633P	20001114 (60)
	US 2000-247632P	20001114 (60)
	US 2000-247631P	20001114 (60)
	US 2000-247630P	20001114 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Robert M. Schulman, Esq., Hunton & Williams, Suite 1200, 1900 K Street, N.W., Washington, DC, 20006-1100
NUMBER OF CLAIMS: 40
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 8 Drawing Page(s)
LINE COUNT: 2048
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . pharmaceutically acceptable excipient. The microencapsulating agent can be selected from polyethylene glycol (PEG), an amino acid, a sugar and a **salt**. When an adjuvant is included in the composition, the adjuvant preferably activates an intestinal transporter.

DETD . . . the composition has the potential of stabilizing the polypeptide further. Stabilizers such as sugar, amino acids, polyethylene glycol (PEG) and **salts** have been shown to prevent protein unfolding. In another embodiment of the invention, a pre-first order release of the active agent is imparted by microencapsulating the carrier polypeptide-active agent conjugate in a polysaccharide, amino acid complex, PEG or **salts**.

DETD . . . may be suitable for the drug alcohol of choice. For example, a suspension of glutamic acid, the alcohol and concentrated **hydrochloric acid** can be prepared and heated for several hours. The .gamma.-alkyl glutamate product can be precipitated out in acetone, filtered, dried. . .

DETD . . . pKb. Sodium acetate was the preferred reagent because its pKb is between that of sodium bromide, polyglutamic acid, and sodium **salt**. The reaction using basic alumina kept the T.sub.4-NCA and T.sub.3-NCA intact with no apparent capping or self-polymerization. The stability of. . .

DETD [0077] Experimentation with several weak bases revealed that a variety of sodium **salts** of a carboxylic acid work in capping polyglutamic acid. The reaction was tried with sodium propionate, sodium butyrate, and sodium. . .

DETD . . . splitting the reaction. The Mass range was determined from MALDI. The yield over 100% could reflect either the presence of **salts** or uneven distribution when the reaction mixture was split.

DETD . . . (360 MHz, CDCl.sub.3) .delta. 6.677 (d, 1H, naltrexone aromatic), 6.591 (d, 1H, naltrexone aromatic), 3.874 (s, 3H, methoxy group.), 0.6-0.5 **ppm** (m, 2H, naltrexone cyclopropyl) and 0.2-0.1 **ppm** (m, 2H, naltrexone cyclopropyl).

DETD . . . (d, 1H, naltrexone aromatic), 4.3-4.2 (m, 1H, glutamic acid .alpha.-proton), 1.7-1.3 (pair of bs, 18H, Boc and OtBu groups.), 0.6-0.4 **ppm** (m, 2H, naltrexone cyclopropyl) and 0.2-0.0 **ppm** (m, 2H, naltrexone cyclopropyl).

DETD . . . (d, 1H, naltrexone aromatic), 4.6-4.5 (m, 1H, aspartic acid .alpha.-proton), 1.6-1.3 (pair of bs, 18H, Boc and OtBu groups.), 0.7-0.5 **ppm** (m, 2H, naltrexone cyclopropyl) and 0.4-0.1 **ppm** (m, 2H, naltrexone cyclopropyl).

DETD . . . ml) was stirred at ambient temperatures for 2 hours. Solvent was removed to obtain glu(acetaminophen) (0.90 g) as the HCl **salt**: .sup.1H NMR (D.sub.2O) .delta. 2.19 (s, 3H, acetaminophen CH.sub.3), 2.41 (m, 2H, Glu-.beta. H), 2.97 (t, 2H, Glu-.gamma. H), 4.18. . .

DETD [0160] This material was dissolved in 1.5 ml dry anisole and stirred with 0.3 ml anhydrous **methanesulfonic acid** for 3 h upon which another 0.3 ml anhydrous **methanesulfonic acid** was added and the solution stirred for 1 h. The reaction mixture was poured into 6 ml Et.sub.2O and refrigerated. . .

DETD [0163] The protected polymer was dissolved in 1.5 ml dry anisole and stirred with 1.3 ml anhyd **methanesulfonic acid** for 4 h. The solution was concentrated to 0.5 ml by rotary evaporation. Et.sub.2O (8 ml) was added and the. . .

CLM What is claimed is:

. . . said microencapsulating agent is selected from the group consisting of polyethylene glycol (PEG), an amino acid, a sugar and a **salt** .

IT 50-06-6, Phenobarbital, biological studies 50-18-0, Cyclophosphamide 50-35-1, Thalidomide 50-44-2, Mercaptopurine 50-78-2, Acetylsalicylic acid 50-81-7, Vitamin C, biological studies 51-21-8, Fluorouracil 51-61-6, Dopamine, biological studies 51-63-8, Dextroamphetamine sulfate 51-98-9, Norethindrone acetate 52-01-7, Spironolactone 52-24-4, Thiotepa 52-86-8, Haloperidol 53-36-1, Methylprednisolone Acetate 54-31-9, Furosemide 55-63-0, Nitroglycerin 57-63-6, Ethinyl estradiol 58-08-2, Caffeine, biological studies 58-18-4, Methyltestosterone 58-25-3, Chlordiazepoxide 58-33-3, Promethazine hydrochloride 58-55-9, Theophylline, biological studies 58-61-7, Adenosine, biological studies 58-93-5, Hydrochlorothiazide 59-42-7, Phenylephrine 60-54-8, Tetracycline 60-87-7, Promethazine 64-31-3, Morphine Sulfate 67-20-9, Nitrofurantoin 67-92-5, Dicyclomine hydrochloride 68-19-9, Vitamin B12 68-22-4, Norethindrone 71-58-9, Medroxyprogesterone acetate 71-68-1, Hydromorphone hydrochloride 74-79-3, Arginine, biological studies 76-41-5, Oxymorphone 76-42-6, Oxycodone 76-58-4, Ethylmorphine 78-44-4, Carisoprodol 84-02-6, Prochlorperazine maleate 87-08-1, Penicillin V 87-33-2, Isosorbide Dinitrate 89-57-6, Mesalamine 90-82-4, Pseudoephedrine 93-14-1,

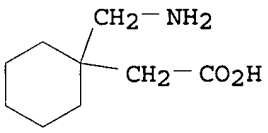
Guaifenesin 113-45-1, Methylphenidate 113-52-0 113-92-8, Chlorpheniramine maleate 114-07-8, Erythromycin 124-90-3, Oxycodone hydrochloride 125-28-0, Dihydrocodeine 125-29-1, Hydrocodone 125-33-7, Primidone 125-71-3, Dextromethorphan 128-13-2, Ursodiol 129-06-6, Warfarin Sodium 132-17-2, Benzatropine methanesulfonate 143-52-2, Methyldihydromorphinone 143-71-5, Hydrocodone bitartrate 152-11-4, Verapamil hydrochloride 297-76-7, Ethynodiol diacetate 298-46-4, Carbamazepine 298-59-9, Methylphenidate hydrochloride 303-49-1, Clomipramine 315-30-0, Allopurinol 318-98-9, Propranolol Hydrochloride 378-44-9, Betamethasone 379-79-3, Ergotamine Tartrate 437-38-7, Fentanyl 439-14-5, Diazepam 446-86-6, Azathioprine 466-99-9, Hydromorphone 469-62-5, Propoxyphene 509-60-4, Dihydromorphine 514-36-3, Fludrocortisone acetate 541-15-1, Levocarnitine 549-18-8, Amitriptyline hydrochloride 554-13-2, Lithium Carbonate 561-27-3, Diacetylmorphine 595-33-5, Megestrol acetate 604-75-1, Oxazepam 630-93-3, Sodium phenytoin 657-24-9, Metformin 745-65-3, Alprostadil 747-36-4, Hydroxychloroquine sulfate 797-63-7, Levonorgestrel 846-49-1, Lorazepam 846-50-4, Temazepam 894-71-3, Nortriptyline hydrochloride 959-24-0, Sotalol hydrochloride 1134-47-0, Baclofen 1403-66-3, Gentamicin 1404-93-9, Vancomycin hydrochloride 1501-84-4, Rimantadine hydrochloride 1508-65-2, Oxybutynin chloride 1622-61-3, Clonazepam 1665-48-1, Metaxalone 1744-22-5, Riluzole 1951-25-3, Amiodarone 2078-54-8, Propofol 2152-34-3, Pemoline 2375-03-3, Methylprednisolone sodium succinate 4205-91-8 4682-36-4, Orphenadrine citrate 4759-48-2, Isotretinoin 5786-21-0, Clozapine 6202-23-9, Cyclobenzaprine hydrochloride 6493-05-6, Pentoxifylline 6533-00-2, Norgestrel 7280-37-7, Estropipate 7414-83-7, Etidronate disodium 9002-60-2, Adrenocorticotrophic hormone, biological studies 9002-69-1, Relaxin 9005-49-6, Heparin, biological studies 9014-42-0, Thrombopoietin 9039-53-6, Urokinase 9041-08-1, Dalteparin sodium 9041-92-3, ..alpha..1-Protease inhibitor 9080-79-9, Sodium polystyrene sulfonate 10238-21-8, Glyburide 11005-12-2, .beta.-Phytosterol 11056-06-7, Bleomycin 11140-85-5, Glucagon hydrochloride 13311-84-7, Flutamide 13614-98-7, Minocycline hydrochloride 14124-50-6, Hydrochlorothiazide-triamterene mixt. 14611-52-0, Selegiline hydrochloride 14838-15-4, Phenylpropanolamine 15307-79-6, Diclofenac sodium 15663-27-1, Cisplatin 15686-71-2, Cephalexin 17140-78-2, Propoxyphene napsylate 17560-51-9, Metolazone 18559-94-9, Albuterol 19767-45-4, Mesna 20537-88-6, Amifostine 20830-75-5, Digoxin 21062-37-3D, analogs 21256-18-8, Oxaprozin 21829-25-4, Nifedipine 22071-15-4, Ketoprofen 23031-32-5, Terbutaline sulfate 25316-40-9, Doxorubicin hydrochloride 25322-68-3, Polyethylene glycol 25332-39-2, Trazodone hydrochloride 25614-03-3, Bromocriptine 26159-34-2, Naproxen sodium 26787-78-0, Amoxicillin 27164-46-1, Cefazolin sodium 27314-97-2, Tirapazamine 28860-95-9, Carbidopa 28981-97-7, Alprazolam 29094-61-9, Glipizide 29354-16-3, Thyronine, iodo- 31677-93-7, Bupropion hydrochloride 32222-06-3, Calcitriol 32780-64-6, Labetalol hydrochloride 33069-62-4, Paclitaxel 33286-22-5, Diltiazem hydrochloride 33419-42-0, Etoposide 33564-30-6, Cefoxitin sodium 34552-83-5, Loperamide hydrochloride 34580-13-7, Ketotifen 35189-28-7, Norgestimate 36282-47-0, Tramadol hydrochloride 36505-84-7, Buspirone 36791-04-5, Ribavirin 37296-80-3, Colestipol hydrochloride 38398-32-2, Ganaxolone 41340-25-4, Etodolac 41575-94-4, Carboplatin 42200-33-9, Nadolol 42617-41-4, Activated protein C 42924-53-8, Nabumetone 49562-28-9, Fenofibrate 49842-07-1, Tobramycin sulfate 50370-12-2, Cefadroxil 50700-72-6, Vecuronium bromide 51321-79-0, Sparfosic acid 51481-61-9, Cimetidine 51773-92-3, Mefloquine

hydrochloride 52232-67-4, Teriparatide 53885-35-1, Ticlopidine hydrochloride 53994-73-3, Cefaclor 54024-22-5, Desogestrel 54143-56-5, Flecainide acetate 54182-58-0, Sucralfate 54910-89-3, Fluoxetine 54965-24-1, Tamoxifen citrate 55079-83-9, Acitretin 56180-94-0, Acarbose 56238-63-2, Cefuroxime sodium 57109-90-7, Clorazepate dipotassium 57248-88-1, Pamidronate disodium 57852-57-0, Idarubicin hydrochloride 58579-51-4, Anagrelide hydrochloride 58786-99-5, Butorphanol tartrate 59122-46-2, Misoprostol 59703-84-3, Piperacillin sodium 59729-32-7, Citalopram hydrobromide 59865-13-3, Cyclosporin 59989-18-3, Eniluracil **60142-96-3**, Gabapentin 60205-81-4, Ipratropium 60748-06-3, Gastrin 17 61718-82-9, Fluvoxamine maleate 62288-83-9, Desmopressin acetate 62571-86-2, Captopril 63074-08-8, Terazosin hydrochloride 63675-72-9, Nisoldipine 64221-86-9, Imipenem 64461-82-1, Tizanidine hydrochloride 64485-93-4, Cefotaxime sodium 64544-07-6, Cefuroxime axetil 65277-42-1, Ketoconazole 65646-68-6, Fenretinide 65807-02-5, Goserelin 66085-59-4, Nimodipine 66104-22-1, Pergolide 66357-35-5, Ranitidine 66722-44-9, Bisoprolol 67889-72-9, Acetaminophen-codeine phosphate mixt. 67992-58-9, Sodium ioxaglate 68562-41-4, Mecasermin 68693-11-8, Modafinil 68844-77-9, Astemizole 69655-05-6, Didanosine 70458-96-7, Norfloxacin 70476-82-3, Mitoxantrone hydrochloride 72509-76-3, Felodipine 72558-82-8, Ceftazidime 72956-09-3, Carvedilol 73334-07-3, Iopromide 73573-87-2, Formoterol 73590-58-6, Omeprazole 74103-06-3, Ketorolac 74191-85-8, Doxazosin 74356-00-6, Cefotetan disodium
(compns. comprising a polypeptide and an active agent)

IT **60142-96-3**, Gabapentin
(compns. comprising a polypeptide and an active agent)

RN 60142-96-3 USPATFULL

CN Cyclohexaneacetic acid, 1-(aminomethyl)- (9CI) (CA INDEX NAME)



L4 ANSWER 5 OF 9 USPATFULL on STN

AB Pharmaceutical compositions containing substantially pure and stable gabapentin are disclosed wherein gabapentin contains an anion of a mineral acid, such as chloride, in amounts greater than 20 **ppm**
.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2002:119942 USPATFULL		
TITLE:	Stable gabapentin containing more than 20 **ppm** of chlorine ion		
INVENTOR(S):	Singer, Claude, Kfar Saba, ISRAEL Pilarsky, Gideon, Holon, ISRAEL Pesachovich, Michael, Givat Shmuel, ISRAEL		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002061931	A1	20020523
	US 6531509	B2	20030311

10/024,339

APPLICATION INFO.: US 2001-880854 A1 20010615 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-211967P	20000616 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: KENYON & KENYON, 1500 K STREET, N.W., SUITE 700, WASHINGTON, DC, 20005
NUMBER OF CLAIMS: 7
EXEMPLARY CLAIM: 1
LINE COUNT: 623
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Stable gabapentin containing more than 20 **ppm** of chlorine ion

AB . . . gabapentin are disclosed wherein gabapentin contains an anion of a mineral acid, such as chloride, in amounts greater than 20 **ppm**.

SUMM . . . the present invention relates to a composition and a process for manufacturing pure and stable gabapentin having greater than 20 **ppm** of chloride ion.

SUMM . . . or less of corresponding lactam, (ii) not allowing the anion of a mineral acid in the composition to exceed 20 **ppm**, and (iii) using a specifically selected adjuvant that is not adverse to gabapentin stability.

SUMM . . . It has now been found that Augart's reliance on maintaining the anion of a mineral acid as not exceeding 20 **ppm** is misplaced. Thus, gabapentin and pharmaceutical formulations of gabapentin can be prepared and stored such that initially they do not. . .

SUMM [0010] The specific mineral acid disclosed by Augert is **hydrochloric acid** (column 3, lines 61-63; column 5, lines 24-29; exampes 1 and 2). The specification states, in particular

SUMM [0012] The proportion of remaining hydrochloride admixtures should thereby not exceed 20 **ppm**.

SUMM [0014] 20 **ppm** of gabapentin hydrochloride corresponds to roughly 3 **ppm** of chloride ion, due to the higher molecular weight of gabapentin.

SUMM [0015] Augert's claims require gabapentin with "less than 20 **ppm** of the anion of a mineral acid", e.g. chloride.

SUMM . . . Accordingly, the present invention relates to a pharmaceutical composition containing a pharmaceutically effective amount of gabapentin containing more than 20 **ppm** of an anion of a mineral acid and which initially contains less than 0.5% of a corresponding lactam and after. . .

SUMM . . . The present invention also relates to a process for preparing a stable pharmaceutical formulation containing gabapentin with more than 20 **ppm** of the anion of a mineral acid and which initially contains less than 0.5% of a corresponding lactam and after. . .

SUMM [0019] As will be illustrated through exemplary embodiments 1-16, gabapentin may be prepared from the hydrochloride **salt** of gabapentin (gabapentin hydrochloride) and that in purified form gabapentin may contain more than 20 **ppm** of chloride ion in the composition as measured by the amount of chloride ion in the composition.

SUMM . . . Exemplary embodiments 17-19 illustrate formulations of gabapentin containing varying amounts of chloride ion, some of which are greater than 20 **ppm** and some less, and all of which initially contain less than 0.5% of lactam and after one year of storage. . .

DETD . . . anion content of the above-prepared gabapentin were obtained:

TABLE 1

Anion content and pH values after the reslurry in methanol

Run	Cl (ppm)	pH
A	4	6.94
B	20	7.01
C	<5	7.04
D	40	6.97
E	35	6.92
F	15	6.84

DETD . . . under vacuum resulting in pure gabapentin with a yield of 87%, pH of 7.15 and chlorine anion content of 50 ppm. Gabapentin so prepared contains less than 0.5% by weight of lactam, and, after a year of storage at 25.degree. C.. . .

DETD . . . under vacuum, resulting in pure gabapentin having a yield of 85%, pH of 6.8, and chlorine anion content of 50 ppm. Gabapentin so prepared contained less than 0.5% by weight of lactam, and, after a year of storage at 25.degree. C.. . .

DETD . . . reslurry as in Example 1B gabapentin pure was obtained at a yield of 58.8% and chloride anion content of 7 ppm Cl.sup.-.

DETD . . . reslurry as in Example 1B, gabapentin pure was obtained having a yield of 75.0% and chloride anion content of 213 ppm.

DETD . . . process, as in Example 1B, gabapentin pure was obtained having a yield of 68.0% and chloride anion content of 142 ppm.

DETD . . . After reslurry as in Example 1B, gabapentin pure was obtained having a yield of 67.8%, and anion content of 142 ppm.

DETD . . . After reslurry as in Example 1B, gabapentin pure was obtained, having a yield of 57.9%, and anion content of 142 ppm.

DETD . . . reslurry as in Example 1B, gabapentin pure was obtained having a yield of 57.9% and an anion content of 142 ppm.

DETD . . . values were obtained and tabulated in TABLE 2 as follows:

TABLE 2

Anion content and PH values for crystallization in methanol

Run	Cl (ppm)	pH
A	4	6.94
B	<5	72
C	150-200	6.9

DETD [0058] 35 ppm.

DETD . . . under vacuum to give gabapentin pure at a yield of 81.4%, pH of 7.08 and anion content of Cl.sup.- 20 ppm.

DETD . . . under vacuum to give gabapentin pure having a yield of 72.4%, pH of 7.28 and anion (Cl.sup.-) content of 20 ppm.

DETD . . . under vacuum to give gabapentin pure having a yield of 75.8%, pH of 7.03 and anion content of (Cl.sup.-) 20 ppm.

DETD . . . under vacuum to give gabapentin pure having a yield of 77.6%, pH of 7.22 and anion (Cl.sup.-) content of 20 ppm.

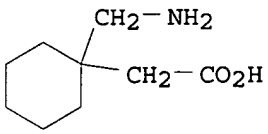
DETD . . . under vacuum to give gabapentin pure having a yield of 75%, pH of 7.17 and anion content (Cl.sup.-) of 10 ppm.

DETD [0073] The following gabapentin tablet formulation is prepared using gabapentin containing chloride ion ranging from 5 to 40 ppm and pH in the range of 6.84-7.04 according to Example 1. The following material is used:

Ingredients Amounts

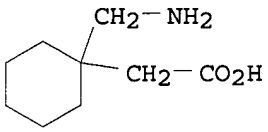
. . .
DETD [0076] Gabapentin of Example 2 (having chloride ion content of 50 **ppm** and pH of 7.15) is used to formulate tablets as in EXAMPLE 17, except that corn starch is replaced in. . .
DETD . . . gabapentin tablet of each sample is initially measured to have 0.5% by weight of a corresponding lactam, more than 50 **ppm** of chloride anion, and pH exceeding 6.8. The tablet is stored for one year at 25.degree. C. and 60% atmospheric. . .
DETD [0078] EXAMPLE 18 is repeated except that gabapentin of Example 4, having chloride ion of 7 **ppm** is used for formulating tablets. The resulting gabapentin tablet of each sample is initially measured to have 0.5% by weight of lactam and approximately 7 **ppm** of chloride anion. The tablet is stored for one year at 55.degree. C. and 50% atmospheric humidity and the increase. . .
DETD . . . show that, contrary to Augart's disclosure, the presence of anion of a mineral acid in an amount greater than 20 **ppm** does not adversely affect the stability of gabapentin when stored for one year at 25.degree. C. and 60% humidity. The. . .
CLM What is claimed is:
. . . composition comprising gabapentin and initially containing less than 0.5% by weight of a corresponding lactam and having greater than 20 **ppm** of an anion of a mineral acid, which, after one year of storage at 25.degree. C. and 60% humidity the. . .
. . . The pharmaceutical composition of claim 1, wherein the amount of said anion of a mineral acid does not exceed 100 **ppm**.

7. Gabapentin which contains less than 0.5% of the corresponding lactam and between 20 and 100 **ppm** of the anion of a mineral acid and which, after one year of storage at 25.degree. C. and 60% humidity. . .
. . . least one adjuvant, and initially containing less than 0.5% by weight of a corresponding lactam and having greater than 20 **ppm** of chloride, which, after one year of storage at 25.degree. C. and 60% humidity the conversion of gabapentin to its. . .
IT 63-42-3, Lactose 79-41-4D, Methacrylic acid, esters, polymers 5415-98-5D, polymers with methacrylates 7631-86-9, Silica, biological studies 9003-39-8, PVP 9004-65-3, HPMC 9005-25-8, Starch, biological studies 9063-38-1, Sodium starch glycolate 12619-70-4, Cyclodextrin 13463-67-7, Titanium oxide, biological studies 14807-96-6, Talc, biological studies 16887-00-6, Chloride, biological studies **60142-95-2**, Gabapentin hydrochloride **60142-96-3**, Gabapentin 74811-65-7, Sodium croscarmellose 77538-19-3, Glyceryl behenate 106392-12-5, Poloxamer
(stable gabapentin contg. more than 20 ppm chloride)
IT **60142-95-2**, Gabapentin hydrochloride **60142-96-3**, Gabapentin
(stable gabapentin contg. more than 20 ppm chloride)
RN 60142-95-2 USPATFULL
CN Cyclohexaneacetic acid, 1-(aminomethyl)-, hydrochloride (9CI) (CA INDEX NAME)



● HCl

RN 60142-96-3 USPATFULL
CN Cyclohexaneacetic acid, 1-(aminomethyl)- (9CI) (CA INDEX NAME)



L4 ANSWER 6 OF 9 USPATFULL on STN
AB A pharmaceutical composition containing substantially pure and stable gabapentin are disclosed wherein gabapentin has a pH of between 6.8 to 7.3.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2002:85616 USPATFULL		
TITLE:	Stable gabapentin having pH within a controlled range		
INVENTOR(S):	Singer, Claude, Kfar Saba, ISRAEL Pilarski, Gideon, Holon, ISRAEL Pesachovich, Michael, Givat Shmuel, ISRAEL		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002045662	A1	20020418
APPLICATION INFO.:	US 2001-880922	A1	20010615 (9)
	NUMBER		DATE
PRIORITY INFORMATION:	US 2000-211966P		20000616 (60)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	KENYON & KENYON, 1500 K STREET, N.W., SUITE 700, WASHINGTON, DC, 20005		
NUMBER OF CLAIMS:	5		
EXEMPLARY CLAIM:	1		
LINE COUNT:	622		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . or less of corresponding lactam, (ii) not allowing the anion of a mineral acid in the composition to exceed 20 **ppm**, and (iii) using a specifically selected adjuvant that is not adverse to gabapentin stability.
SUMM . . . It has now been found that Augart's reliance on maintaining the anion of a mineral acid as not exceeding 20 **ppm** is misplaced. Thus, gabapentin and pharmaceutical formulations of gabapentin can be

prepared and stored such that initially they do not. . .

SUMM [0012] The specific mineral acid disclosed by Augert is **hydrochloric acid** (column 3, lines 61-63; column 5, lines 24-29; exampes 1 and 2). The specification states, in particular

SUMM . . . for example, from the corresponding hydrochloride by ion exchange. The proportion of remaining hydrochloride admixtures should thereby not exceed 20 **ppm**.

SUMM [0015] 20 **ppm** of gabapentin hydrochloride corresponds to roughly 3 **ppm** of chloride ion, due to the higher molecular weight of gabapentin.

SUMM [0016] Augert's claims require gabapentin with "less than 20 **ppm** of the anion of a mineral acid", e.g. chloride.

SUMM [0020] As will be illustrated through exemplary embodiments 1-16, gabapentin may be prepared from the hydrochloride **salt** of gabapentin (gabapentin hydrochloride) and that in purified form gabapentin may have a pH in the range of 6.8-7.3, and preferably in the range of 7.0-7.2. The gabapentin formulation may also contain more than 20 **ppm** of chloride ion in the composition as measured by the amount of chloride ion in the composition.

SUMM . . . Exemplary embodiments 17-19 illustrate formulations of gabapentin containing varying amounts of chloride ion, some of which are greater than 20 **ppm** and some less, and all of which initially contain less than 0.5% of lactam and after one year of storage. . .

DETD . . . chlorine anion content of the above-prepared gabapentin were obtained:

TABLE 1

Anion content and PH values after the reslurry in methanol

Run	Cl.sup.-(**ppm**)	pH
A	4	6.94
B	20	7.01
C	<5	7.04
D	40	6.97
E	35	6.92
F	15	6.84

DETD . . . under vacuum resulting in pure gabapentin with a yield of 87%, pH of 7.15 and chlorine anion content of 50 **ppm**. Gabapentin so prepared initially contained less than 0.5% by weight of lactam, and, after a year of storage at 25.degree.. . .

DETD . . . under vacuum, resulting in pure gabapentin having a yield of 85%, pH of 6.8, and chlorine anion content of 50 **ppm**. Gabapentin so prepared contained less than 0.5% by weight of lactam, and, after a year of storage at 25.degree. C.. . .

DETD . . . reslurry as in Example 1B gabapentin pure was obtained at a yield of 58.8% and chloride anion content of 7 **ppm** Cl.sup.-.

DETD . . . reslurry as in Example 1B, gabapentin pure was obtained having a yield of 75.0% and chloride anion content of 213 **ppm**.

DETD . . . process, as in Example 1B, gabapentin pure was obtained having a yield of 68.0% and chloride anion content of 142 **ppm**.

DETD . . . After reslurry as in Example 1B, gabapentin pure was obtained having a yield of 67.8%, and anion content of 142 **ppm**.

DETD . . . After reslurry as in Example 1B, gabapentin pure was obtained, having a yield of 57.9%, and anion content of 142 **ppm**.

DETD . . . reslurry as in Example 1B, gabapentin pure was obtained having a yield of 57.9% and an anion content of 142 **ppm**.

DETD . . . values were obtained and tabulated in TABLE 2 as follows:

TABLE 2

Anion content and PH values for crystallization in methanol

Run	Cl (ppm)	pH
A	4	6.94
B	<5	7.2
C	150-200	6.9

DETD . . . under vacuum to give gabapentin pure having a yield of 81.4%, pH of 7.25 and chlorine anion content of 35 **ppm**.

DETD . . . under vacuum to give gabapentin pure at a yield of 81.4%, pH of 7.08 and anion content of Cl.sup.- 20 **ppm**.

DETD . . . under vacuum to give gabapentin pure having a yield of 72.4%, pH of 7.28 and anion (Cl.sup.-) content of 20 **ppm**.

DETD . . . under vacuum to give gabapentin pure having a yield of 75.8%, pH of 7.03 and anion content of (Cl.sup.-) 20 **ppm**.

DETD . . . under vacuum to give gabapentin pure having a yield of 77.6%, pH of 7.22 and anion (Cl.sup.-) content of 20 **ppm**.

DETD . . . under vacuum to give gabapentin pure having a yield of 75%, pH of 7.17 and anion content (Cl.sup.-) of 10 **ppm**.

DETD [0077] The following gabapentin tablet formulation is prepared using gabapentin containing chloride ion ranging from 5 to 40 **ppm** and pH in the range of 6.84-7.04 according to Example 1. The following material is used:

Ingredients	Amounts

. . .

DETD [0080] Gabapentin of Example 2 (having chloride ion content of 50 **ppm** and pH of 7.15) is used to formulate tablets as in EXAMPLE 17, except that corn starch is replaced in. . .

DETD . . . gabapentin tablet of each sample is initially measured to have 0.5% by weight of a corresponding lactam, more than 50 **ppm** of chloride anion, and pH exceeding 6.8. The tablet is stored for one year at 25.degree. C. and 60% atmospheric. . .

DETD [0082] EXAMPLE 18 is repeated except that gabapentin of Example 4, having chloride ion of 7 **ppm** is used for formulating tablets. The resulting gabapentin tablet of each sample is initially measured to have 0.5% by weight of lactam and approximately 7 **ppm** of chloride anion. The tablet is stored for one year at 25.degree. C. and 60% atmospheric humidity and the increase. . .

DETD . . . show that, contrary to Augart's disclosure, the presence of anion of a mineral acid in an amount greater than 20 **ppm** does not adversely affect the stability of gabapentin when stored for one year at 25.degree. C. and 60% humidity (or. . .

CLM What is claimed is:

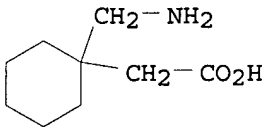
5. Gabapentin which contains less than 0.5% of the corresponding lactam, and less than 100 **ppm** of the anion of a mineral acid, which has a pH between 6.8 and 7.3, and which, after one year. . .

IT **60142-96-3P**, Gabapentin
(stable gabapentin having pH within a controlled range)

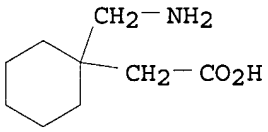
IT **60142-95-2**, Gabapentin hydrochloride
(stable gabapentin having pH within a controlled range)

IT **60142-96-3P**, Gabapentin

(stable gabapentin having pH within a controlled range)
RN 60142-96-3 USPATFULL
CN Cyclohexaneacetic acid, 1-(aminomethyl)- (9CI) (CA INDEX NAME)



IT **60142-95-2**, Gabapentin hydrochloride
(stable gabapentin having pH within a controlled range)
RN 60142-95-2 USPATFULL
CN Cyclohexaneacetic acid, 1-(aminomethyl)-, hydrochloride (9CI) (CA INDEX NAME)



● HCl

L4 ANSWER 7 OF 9 USPATFULL on STN
AB The present invention concerns cyclic amino acids of formula ##STR1## substantially free from the lactam ##STR2## wherein n is an integer of from 4 to 6, a process for the preparation thereof, compositions containing the compounds and methods of using them.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2000:50732 USPATFULL
TITLE:	Lactam-free amino acids
INVENTOR(S):	Augart, Helmut, Waldkirch, Germany, Federal Republic of Gebhardt, Uwe, Waldkirch, Germany, Federal Republic of Herrmann, Wolfgang, Merzhausen, Germany, Federal Republic of
PATENT ASSIGNEE(S):	Godecke Aktiengesellschaft, Berlin, Germany, Federal Republic of (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6054482		20000425
APPLICATION INFO.:	US 1995-377618		19950125 (8)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1993-20270, filed on 18 Feb 1993, now abandoned which is a continuation of Ser. No. US 1992-865723, filed on 8 Apr 1992, now abandoned which is a continuation of Ser. No. US 1990-570500, filed on 21 Aug 1990, now abandoned

NUMBER	DATE

PRIORITY INFORMATION:	DE 1989-3928183	19890825
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	Granted	
PRIMARY EXAMINER:	Shippen, Michael L.	
LEGAL REPRESENTATIVE:	Tinney, Francis J.	
NUMBER OF CLAIMS:	11	
EXEMPLARY CLAIM:	1,7	
LINE COUNT:	301	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . and cranial traumas. U.S. Pat. Nos. 4,024,175 and 4,087,544 cover the compound and its uses. They also disclose an acid **salt**, i.e., gabapentin hydrochloride hydrate, in a ratio of 4:4:1 and a sodium **salt** of gabapentin hydrate in a ratio of 2:1.

SUMM . . . is a hydrogen atom or a lower alkyl radical and n is 4, 5, or 6 and the pharmaceutically acceptable **salts** thereof, which depend upon known methods used for the preparation of primary amines or amino acid.

SUMM The instant invention covers a compound of formula ##STR5## or a pharmaceutically acceptable **salt** thereof substantially free from ##STR6## wherein n is an integer of from 4 to 6.

SUMM (c) converting the product of step (b) to a pharmaceutically acceptable **salt** thereof, if desired.

SUMM A preferred process of the instant invention is one wherein the mineral **acid hydrochloric acid** is used and an ion exchanger is used for anion removal.

SUMM . . . hydrogen atom or lower alkyl and n is an integer 4, 5 or 6, as well as the pharmacologically acceptable **salts** thereof. These compounds possess valuable pharmacodynamic properties. The compounds of formula (I) have an extraordinarily low toxicity. In animal experiments,. . .

SUMM . . . converted by esterification into a lower alkyl ester or by reaction with an acid or base into a pharmacologically acceptable **salt**.

SUMM The hydrochloride of gabapentin was the most suitable form of the active material since **salts** and especially hydrochlorides as a rule usually provide especially good stability and good solubility. However, in some cases, pharmaceutical compositions. . .

SUMM . . . for example, from the corresponding hydrochloride by ion exchange. The proportion of remaining hydrochloride admixtures should thereby not exceed 20 **ppm**. The same also applies to other mineral acids.

DETD 22.3 L of water and 22.3 L of concentrated **hydrochloric acid** are mixed in a T100 reactor and 6.41 kg gabapentin lactam added while stirring. The clear brown solution formed is. . .

CLM What is claimed:

. . . 0.5% by weight of a compound of Formula VIII ##STR18## wherein n is as defined above and less than 20 **ppm** of an anion of a mineral acid comprising: (a) hydrolysis of a compound of Formula VII containing a compound of. . . VIII alone with a mixture of equal volumes of a concentrated mineral acid and water to afford an acid addition **salt** of a compound of Formula VII and (b) converting the acid addition **salt** of a compound of Formula VII by ion exchange to a compound of Formula VII containing less than 0.5% by weight of a compound of Formula VIII and less than 20 **ppm** of an anion of a mineral acid.

2. A process according to claim 1, wherein in step (a) the **acid**

is **hydrochloric acid**.

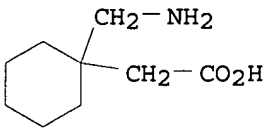
3. A process for preparing stable and pure pharmaceutical compositions containing a compound of formula (VII) ##STR19## wherein n is. . . VIII alone with a mixture of equal volumes of a concentrated mineral acid and water to afford an acid addition **salt** of a compound of formula VII substantially free of a compound of formula VIII, (b) converting the acid addition **salt** of a compound of formula VII by ion exchange to a compound of formula VII containing less than 0.5% by. . . of a compound of formula VIII, wherein the proportion of remaining anion of a mineral acid does not exceed 20 **ppm**, (c) adding pharmaceutically acceptable adjuvants to form a pharmaceutical composition wherein the adjuvants do not promote the formation of a. . .

5. A process of claim 3, wherein the mineral **acid** is **hydrochloric acid**.

7. A stable and pure pharmaceutical composition in unit dry medicinal dosage form consisting essentially of: (i) an active ingredient. . . free amino acid, crystalline anhydrous form containing less than 0.5% by weight of its corresponding lactam and less than 20 **ppm** of an anion of a mineral acid and (ii) one or more pharmaceutically acceptable adjuvants that do not promote conversion. . .

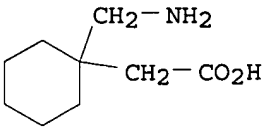
11. A pharmaceutical composition according to claim 7,wherein in (i) the mineral **acid** is **hydrochloric acid**.

IT **60142-95-2P**
(prepn. and conversion of, to free base)
IT **60142-96-3P**
(prepn. of, from gabapentin lactam)
IT **60142-95-2P**
(prepn. and conversion of, to free base)
RN 60142-95-2 USPATFULL
CN Cyclohexaneacetic acid, 1-(aminomethyl)-, hydrochloride (9CI) (CA INDEX NAME)



HCl

IT **60142-96-3P**
(prepn. of, from gabapentin lactam)
RN 60142-96-3 USPATFULL
CN Cyclohexaneacetic acid, 1-(aminomethyl)- (9CI) (CA INDEX NAME)



L4 ANSWER 8 OF 9 USPATFULL on STN

AB A novel crystalline form of gabapentin and a novel processes for the small and large scale preparations of the anticonvulsant compound in a highly pure state is disclosed. This novel hydrate is produced by a cost effective process which provides an additional purification stage.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	90:76869 USPATFULL
TITLE:	Gabapentin mohohydrate and a process for producing the same
INVENTOR(S):	Butler, Donald E., Holland, MI, United States Greenman, Barbara J., Door, MI, United States
PATENT ASSIGNEE(S):	Warner-Lambert Company, Morris Plains, NJ, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4960931		19901002
APPLICATION INFO.:	US 1989-417995		19891006 (7)
RELATED APPLN. INFO.:	Division of Ser. No. US 1988-188819, filed on 2 May 1988, now patented, Pat. No. US 4894476		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Shippen, Michael L.		
LEGAL REPRESENTATIVE:	Anderson, Elizabeth M.		
NUMBER OF CLAIMS:	7		
EXEMPLARY CLAIM:	1,7		
LINE COUNT:	295		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . and cranial traumas. U.S. Pat. Nos. 4,024,175 and 4,087,544 cover the compound and its uses. They also disclose an acid **salt**, i.e. gabapentin.hydrochloride hydrate in a ratio of 4:4:1 and a sodium **salt** of gabapentin hydrate in a ratio of 2:1. These patents are hereby incorporated by reference.

SUMM . . . is a hydrogen atom or a lower alkyl radical and n is 4, 5, or 6 and the pharmaceutically acceptable **salts** thereof, which depend upon known methods used for the preparation of primary amines or amino acids.

SUMM . . . into the desired (1-aminomethyl)-1-cyclohexaneacetic acid by acidic hydrolysis (preferred) to give an acid or basic hydrolysis to give a basic **salt** or followed by acidification to give an acid **salt**.

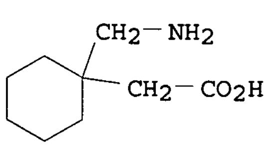
SUMM (a) pouring a 1 N solution of an acid **salt** of (1-aminomethyl)-cyclohexaneacetic acid onto an ion exchange column in the basic form and eluting that column with deionized water;

SUMM Useful acid **salts** are hydrobromide, sulphate, methane sulfonate, hydrochloride and the like. The preferred acid **salt** in step (a) is the hydrochloride.

SUMM (a) pouring a solution of an acid **salt** of (1-aminomethyl)-cyclohexaneacetic acid in deionized water onto an ion exchange column in

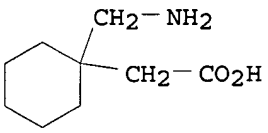
the basic form and eluting the column with. . . .
SUMM Useful acid **salts** include but are not limited to hydrobromide, sulphate, methanesulfonate, hydrochloride and the like. The preferred **salt** is the hydrochloride and in a preferred ratio is 4:4:1.
SUMM The preferred acid **salt** of (1-aminomethyl)-cyclohexaneacetic acid is the monohydrochloride hydrate in a ratio of 4:4:1.
SUMM . . . of this kind include, for example, tartrate and citrate buffers, ethanol, complex-forming agents (such as ethylenediamine-tetraacetic acid and the nontoxic **salts** thereof), as well as high molecular weight polymers (such as liquid polyethylene oxide) for viscosity regulation. Solid carrier materials include,. . .
DETD CL.sup.- : 8.6 **ppm**
DETD . . . The resin is treated with 3700 L of filtered deionized water that has been mixed with 60.6 Kg of concentrated **hydrochloric acid**. The **acid** treatment is repeated with fresh acid.
The resin is washed with 6400 L of filtered deionized water. The resin is. . .
DETD The resin is treated with 3700 L of filtered deionized water that has been mixed with 60.6 Kg of concentrated **hydrochloric acid**. The **acid** treatment is repeated with fresh acid.
The resin is washed with 6400 L of filtered deionized water. The resin is. . .
DETD The resin is treated with 3700 L of filtered deionized water that has been mixed with 60.6 Kg of concentrated **hydrochloric acid**. The **acid** treatment is repeated with fresh acid.
The resin is washed with 6400 L of filtered deionized water. The resin is. . .
DETD CL.sup.- : 30 **ppm**
DETD CL.sup.- : 22 **ppm**
CLM What is claimed is:
. . . A process for the preparation of a compound of formula ##STR6## which comprises: (a) pouring a solution of an acid **salt** of (1-aminomethyl)-cyclohexaneacetic acid in deionized water onto an ion exchange column in the basic form and eluting the column with. . .
2. A process according to claim 1 wherein in step (a) the acid **salt** is gabapentin hydrochloride hydrate (4:4:1).

IT **60142-95-2**, Gabapentin hydrochloride
(gabapentin monohydrate from, pure)
IT **60142-96-3P**
(prepn. of highly pure)
IT **60142-95-2**, Gabapentin hydrochloride
(gabapentin monohydrate from, pure)
RN 60142-95-2 USPATFULL
CN Cyclohexaneacetic acid, 1-(aminomethyl)-, hydrochloride (9CI) (CA INDEX NAME)



● HCl

IT **60142-96-3P**
(prepn. of highly pure)
RN 60142-96-3 USPATFULL
CN Cyclohexaneacetic acid, 1-(aminomethyl)- (9CI) (CA INDEX NAME)



L4 ANSWER 9 OF 9 USPATFULL on STN
AB A novel crystalline form of gabapentin and a novel processes for the small and large scale preparations of the anticonvulsant compound in a highly pure state is disclosed. This novel hydrate is produced by a cost effective process which provides an additional purification stage.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	90:4484 USPATFULL		
TITLE:	Gabapentin monohydrate and a process for producing the same		
INVENTOR(S):	Butler, Donald E., Holland, MI, United States Greenman, Barbara J., Door, MI, United States		
PATENT ASSIGNEE(S):	Warner-Lambert Company, Morris Plains, NJ, United States (U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4894476		19900116
APPLICATION INFO.:	~~US 1988-188~~819		19880502 (7)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Shippen, Michael L.		
LEGAL REPRESENTATIVE:	Anderson, Elizabeth M.		
NUMBER OF CLAIMS:	2		
EXEMPLARY CLAIM:	1		
LINE COUNT:	271		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . and cranial traumas. U.S. Pat. Nos. 4,024,175 and 4,087,544 cover the compound and its uses. They also disclose an acid **salt**, i.e. gabapentin.hydrochloride hydrate in a ratio of 4:4:1 and a sodium **salt** of gabapentin hydrate in a ratio of 2:1. These patents are hereby incorporated by reference.
SUMM . . . is a hydrogen atom or a lower alkyl radical and n is 4, 5, or 6 and the pharmaceutically acceptable **salts** thereof, which depend upon known methods used for the preparation of primary amines or amino acids.
SUMM . . . into the desired (1-aminomethyl)-1-cyclohexaneacetic acid by acidic hydrolysis (preferred) to give an acid or basic hydrolysis to give a basic **salt** or followed by acidification to give an acid **salt**.
SUMM . . . is for the preparation of a compound of formula ##STR3## which comprises: (a) pouring a 1N solution of an acid **salt** of (1-aminomethyl)-cyclohexaneacetic acid onto an ion exchange column in the basic form and eluting that column with deionized water;

SUMM Useful acid **salts** are hydrobromide, sulphate, methane sulfonate, hydrochloride and the like. The preferred acid **salt** in step (a) is the hydrochloride.

SUMM A process for the preparation of a compound of formula ##STR4## which comprises: (a) pouring a solution of an acid **salt** of (1-aminomethyl)-cyclohexaneacetic acid in deionized water onto an ion exchange column in the basic form and eluting the column with. . .

SUMM Useful acid **salts** include but are not limited to hydrobromide, sulphate, methanesulfonate, hydrochloride and the like. The preferred **salt** is the hydrochloride and in a preferred ratio is 4:4:1.

SUMM The preferred acid **salt** of (1-aminomethyl)-cyclohexaneacetic acid is the monohydrochloride hydrate in a ratio of 4:4:1.

SUMM . . . of this kind include, for example, tartrate and citrate buffers, ethanol, complex-forming agents (such as ethylenediamine-tetraacetic acid and the nontoxic **salts** thereof), as well as high molecular weight polymers (such as liquid polyethylene oxide) for viscosity regulation. Solid carrier materials include,. . .

DETD Analytical data: HPLC: 89.27% w/w against dry analytical standard, H.sub.2 O: 9.68%.+-.0.5, mp 156.degree.-156.7.degree. C. (dec), CL.sup.- : 8.6 **ppm**.

DETD . . . The resin is treated with 3700 L of filtered deionized water that has been mixed with 60.6 Kg of concentrated **hydrochloric acid**. The **acid** treatment is repeated with fresh acid.
The resin is washed with 6400 L of filtered deionized water. The resin is. . .

DETD The resin is treated with 3700 L of filtered deionized water that has been mixed with 60.6 Kg of concentrated **hydrochloric acid**. The **acid** treatment is repeated with fresh acid.
The resin is washed with 6400 L of filtered deionized water. The resin is. . .

DETD The resin is treated with 3700 L of filtered deionized water that has been mixed with 60.6 Kg of concentrated **hydrochloric acid**. The **acid** treatment is repeated with fresh acid.
The resin is washed with 6400 L of filtered deionized water. The resin is. . .

DETD . . . data: HPLC: 89.4 w/w against dry reference standard, H.sub.2 O (Karl Fischer): 9.69%.+-.0.5, mp 156.degree.-156.7.degree. C. (dec), CL.sup.- : 30 **ppm**.

DETD . . . data: HPLC: 100.6% w/w against dry analytical standard, H.sub.2 O: 0.09%. CH.sub.3 OH: 0.01%, (CH.sub.3).sub.2 CHOH: 0.01%, CL.sup.- : 22 **ppm**, Melting point: 161.7.degree.-162.6.degree. C. (dec.).

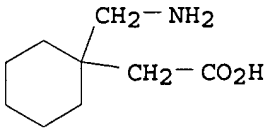
IT **60142-95-2**, Gabapentin hydrochloride
(gabapentin monohydrate from, pure)

IT **60142-96-3P**
(prepn. of highly pure)

IT **60142-95-2**, Gabapentin hydrochloride
(gabapentin monohydrate from, pure)

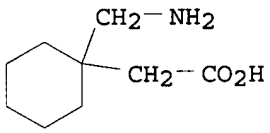
RN 60142-95-2 USPATFULL

CN Cyclohexaneacetic acid, 1-(aminomethyl)-, hydrochloride (9CI) (CA INDEX NAME)



● HCl

IT **60142-96-3P**
(prepn. of highly pure)
RN 60142-96-3 USPATFULL
CN Cyclohexaneacetic acid, 1-(aminomethyl)- (9CI) (CA INDEX NAME)



=> d his

(FILE 'HOME' ENTERED AT 20:11:00 ON 24 OCT 2003)

FILE 'REGISTRY' ENTERED AT 20:11:08 ON 24 OCT 2003
E GABAPENTIN/CN
L1 2 S E3-E4

FILE 'HCAPLUS, USPATFULL' ENTERED AT 20:12:18 ON 24 OCT 2003
L2 97 S L1 AND SALT? AND (HYDROCHLORIC OR HYDROBROMIC? OR HYDROIODIC?
L3 97 DUP REM L2 (0 DUPLICATES REMOVED)
L4 9 S L3 AND PPM

=> s l1 and salt? and (hydrobromic? or hydroiodic? or phosphoric? or nitric? or sulfuric? or sulphuric? or sulfonic? or sulphonic? or methanesulfonic? or methanesulphonic?)(3a)acid?
L5 83 L1 AND SALT? AND (HYDROBROMIC? OR HYDROIODIC? OR PHOSPHORIC? OR NITRIC? OR SULFURIC? OR SULPHURIC? OR SULFONIC? OR SULPHONIC? OR METHANESULFONIC? OR METHANESULPHONIC?)(3A) ACID?

=> dup rem l5
PROCESSING COMPLETED FOR L5
L6 83 DUP REM L5 (0 DUPLICATES REMOVED)

=> s l6 and ppm
L7 2 L6 AND PPM

=> d l7 abs ibib kwic hitstr 1-2

L7 ANSWER 1 OF 2 USPATFULL on STN
AB Stable compositions containing gabapentin compositions, methods of preparing such compositions, and methods of using such compositions.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2003:174060 USPATFULL

TITLE: Stable gabapentin compositions

INVENTOR(S): Cannata, Vincenzo, Sasso Marconi, ITALY
Corcella, Francesco, Rozzano, ITALY
Nicoli, Andrea, Vicenza, ITALY

PATENT ASSIGNEE(S): ZAMBON GROUP S.P.A., Milan, ITALY, 20091 (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003119908	A1	20030626
APPLICATION INFO.:	US 2001-24339	A1	20011221 (10)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: OBLON, SPIVAK, MCCLELLAND, MAIER & NEUSTADT, P.C., 1940 DUKE STREET, ALEXANDRIA, VA, 22314
NUMBER OF CLAIMS: 73
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Page(s)
LINE COUNT: 485

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . describes a method of preparing gabapentin which is free of the gabapentin lactam. These gabapentin compositions contain less than 20 **ppm** of an anion of a mineral acid

SUMM [0008] It is another object of the present invention to provide compositions containing more than 20 **ppm** of an anion of a mineral acid, e.g., chloride.

SUMM . . . Accordingly, the objects of the invention, and others, may be accomplished with a composition comprising gabapentin and at most 5 **ppm**, based on the amount of the gabapentin, of an addition **salt** of gabapentin and an acid.

SUMM [0014] (b) at most 5 **ppm**, based on the amount of the gabapentin, of an addition **salt** of gabapentin and an acid; and

SUMM [0018] (b) at least one **salt** of a nonacidic cation and an anion of a mineral acid, and

SUMM [0020] wherein the composition contains at least 20 **ppm** of the anion of a mineral acid, based on the amount of the gabapentin.

DETD . . . synthesized via the Hofmann rearrangement described in U.S. Pat. No. 4,024,175. Such a process produces a solution of the hydrochloride **salt** of gabapentin. This material may then be extracted or crystallized to produce a gabapentin solution containing 5 and 10 molar. . .

DETD [0030] Content of Acid Addition **Salt** of Gabapentin

DETD [0031] In one embodiment, the composition of the present invention contains gabapentin and at most 5 **ppm**, based on the amount of the gabapentin, of an acid addition **salt** of gabapentin and an acid (hereinafter referred to as "the acid addition **salt**").

DETD [0032] The most relevant acid addition **salt** is gabapentin hydrochloride, i.e., the **salt** of gabapentin and hydrochloric acid. However, the acid may be another mineral **acid** such as **hydrobromic acid**, **hydroiodic acid**, **phosphoric acid**, **nitric acid**, **sulfuric acid**, **sulfonic acid**, or **methanesulfonic acid**.

DETD [0033] The amount of the acid addition **salt** may be lower than 5 **ppm**, such as 4, 3, 2, 1, 0.5, 0.25, 0.1, 0.05 **ppm**

or less.

DETD [0034] It is particularly preferred that the composition contains an undetectable amount of the addition **salt** of hydrochloric acid in a silver nitrate titration assay. This assay may be performed by potentiometrically titrating with 0.01 N. . . . a solution obtained by dissolving 7.5 grams of the composition in 100 mL of methanol/water (80/20 by volume) followed by **acidification** with **nitric acid**. This assay is well-known to those skilled in the art.

DETD [0035] **Salt** of an Nonacidic Cation and an Anion of a Mineral Acid

DETD [0036] In another embodiment, the composition of the present invention gabapentin and at least one **salt** of a nonacidic cation and an anion of a mineral acid, wherein the composition comprises more than 20 **ppm** of the anion of a mineral acid, based on the amount of the gabapentin. As used herein, the term "nonacidic. . . . a Bronsted or a Lewis acid. Thus, the amount of the anion of the mineral acid is higher than 20 **ppm**, such as 25, 30, 40, 50, 75, 100, 250, 500, 1000, 2000, 2500, 3000 **ppm**, or more.

DETD [0037] Such a composition may be prepared, for example, by adding one or more **salts** of of a nonacidic cation and an anion of a mineral acid to the gabapentin produced with less than 5 **ppm** of the acid addition **salt** as described above.

DETD [0038] The composition may also be prepared by adding the appropriate amount of the nonacidic cation hydroxide **salt** (e.g., NaOH) to a sample of gabapentin containing more than 20 **ppm** of chlorides in order to transform the existing chlorides into a **salt** with the nonacidic cation (e.g., NaCl).

DETD [0039] In one embodiment, the composition additionally comprises at most 5 **ppm** of one or more addition **salts** of gabapentin and an acid. The amount of the acid addition **salt** may be lower than 5 **ppm**, such as 4, 3, 2, 1, 0.5, 0.25, 0.1, 0.05 **ppm** or less.

DETD [0043] A preferred anion is chloride. A particularly preferred **salt** is sodium chloride.

DETD [0063] The stbility of a gabapentin compositions containing 60, 70, or 80 **ppm** of gabapentin hydrochloride (GABA-HCl) was measured at 40.degree. C. by HPLC over a period of 3 months. The total amount. . .

DETD [0064] The stbility of a gabapentin compositions which was chloride free, i.e., no GABA-HCl, contained 70 **ppm** of NH.sub.4Cl or 70 **ppm** of GABA-HCl was measured at 40.degree. C. by HPLC over a period of 3 months. The total amount of impurities. . .

DETD . . . The stability of gabapnetin compositions, with respect to gabapentin lactam formation, at 40.degree. C. containing (1) no additives (free of **salts**; denoted reference), (2) 87 **ppm** of NaBr, (3) 50 **ppm** of KCl, (4) 50 **ppm** of Na.sub.2SO.sub.4, (5) 2350 **ppm** of NaCl, (6) 114 **ppm** of HBr, (7) 7 **ppm** of GABA-HCl, or (8) 100 **ppm** of H.sub.2SO.sub.4. The amount of gabapentin lactam produced over 1.5 months was deteremined. The results are shown in FIG. 3. The results of this experiment demonstrated that gabapentin compositions containing a **salt** of a nonacidic cation were quite stable.

DETD [0066] In order to prepare a composition of gabapentin containing 60 **ppm** of chloride (as NaCl), gabapentin (dry, 330 g), demineralized water (165 g), and methanol (218 g) were charged into a. . . resulting solid was then filtered and washed on the filter with 330 g of a NaCl solution in isopropanol/water (308 **ppm**). The product was then dried in an oven at 50.degree. C. for 17 hours. As a

result, gabapentin (307.5 g) was obtained with a chloride content of 60 **ppm** as measured by potentiometric titration with AgNO.sub.3. Gabapentin containing different amounts of chloride (as NaCl), e.g., 70 or 80 **ppm**, can be prepared in a similar fashion.

DETD [0067] In order measure the stability of such compostions, samples prepared as described above containing (1) 60 **ppm** of chloride as NaCl, (2) 80 **ppm** of chloride as NaCl, and (3) 60 **ppm** of chloride as NaCl (duplicate) were stored at 40 C and anlyzed by HPLC to determine the amount of degredation. . .

DETD . . . teaches that the content of an anion of a mineral acid in a gabapentin composition must be less than 20 **ppm**. This experiment demonstrates that no meaningful degredation occurs and the amount of gabapentin lactam remains close to zero.

CLM What is claimed is:

1. A composition comprising gabapentin and at most 5 **ppm**, based on the amount of the gabapentin, of an addition **salt** of gabapentin and an acid.

2. The composition of claim 1, comprising at most 4 **ppm** of the addition **salt** of gabapentin and an acid.

3. The composition of claim 1, comprising at most 3 **ppm** of the addition **salt** of gabapentin and an acid.

4. The composition of claim 1, comprising at most 2 **ppm** of the addition **salt** of gabapentin and an acid.

5. The composition of claim 1, comprising at most 1 **ppm** of the addition **salt** of gabapentin and an acid.

6. The composition of claim 1, comprising at most 0.5 **ppm** of the addition **salt** of gabapentin and an acid.

7. The composition of claim 1, comprising at most 0.25 **ppm** of the addition **salt** of gabapentin and an acid.

8. The composition of claim 1, comprising at most 0.1 **ppm** of the addition **salt** of gabapentin and an acid.

9. The composition of claim 1, comprising at most 0.05 **ppm** of the addition **salt** of gabapentin and an acid.

10. The composition of claim 1, comprising no detectable quantity of the addition **salt** of gabapentin and an acid.

11. The composition of claim 9, which contains no detectable quantity of the addition **salt** of gabapentin by silver nitrate titration.

13. The composition of claim 1, wherein the mineral acid is selected from the group consisting of hydrochloric **acid**, **hydrobromic acid**, **hydroiodic acid**, **phosphoric acid**, **nitric acid**, **sulfuric acid**, **sulfonic acid**, **methanesulfonic acid**.

18. A pharmaceutical composition in dry unit dosage form, comprising: (a) gabapentin; (b) at most 5 **ppm**, based on the amount of the gabapentin, of an addition **salt** of gabapentin and an acid; and

(c) at least one nonacidic pharmaceutically acceptable excipient.

19. A composition, comprising gabapentin and at least one **salt** of a nonacidic cation and an anion of a mineral acid, wherein the composition comprises more than 20 **ppm** of the anion of a mineral acid, based on the amount of the gabapentin.

20. The composition of claim 19, which contains more than 25 **ppm** of the anion of a mineral acid, based on the amount of the gabapentin.

21. The composition of claim 19, which contains more than 30 **ppm** of the anion of a mineral acid, based on the amount of the gabapentin.

22. The composition of claim 19, which contains more than 50 **ppm** of the anion of a mineral acid, based on the amount of the gabapentin.

23. The composition of claim 19, which contains more than 75 **ppm** of the anion of a mineral acid, based on the amount of the gabapentin.

24. The composition of claim 19, which contains more than 100 **ppm** of the anion of a mineral acid, based on the amount of the gabapentin.

25. The composition of claim 19, which contains more than 250 **ppm** of the anion of a mineral acid, based on the amount of the gabapentin.

26. The composition of claim 19, which contains more than 500 **ppm** of the anion of a mineral acid, based on the amount of the gabapentin.

27. The composition of claim 19, which contains more than 1000 **ppm** of the anion of a mineral acid, based on the amount of the gabapentin.

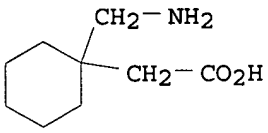
28. The composition of claim 19, which contains more than 2000 **ppm** of the anion of a mineral acid, based on the amount of the gabapentin.

29. The composition of claim 19, comprising at most 5 **ppm** of one or more addition **salts** of gabapentin and an acid.

36. The composition of claim 19, wherein the **salt** is sodium chloride.

37. A pharmaceutical composition in dry unit dosage form, comprising: (a) gabapentin; (b) at least one **salt** of a nonacidic cation and an anion of a mineral acid, and (c) at least one nonacidic excipient wherein the composition contains at least 20 **ppm** of the anion of a mineral acid, based on the amount of the gabapentin.

IT 7647-14-5, Sodium chloride, biological studies **60142-96-3**, Gabapentin
(stable gabapentin compns.)
IT **60142-96-3**, Gabapentin
(stable gabapentin compns.)
RN 60142-96-3 USPATFULL
CN Cyclohexaneacetic acid, 1-(aminomethyl)- (9CI) (CA INDEX NAME)



L7 ANSWER 2 OF 2 USPATFULL on STN

AB A composition comprising a polypeptide and an active agent covalently attached to the polypeptide. Also provided is a method for delivery of an active agent to a patient comprising administering to the patient a composition comprising a polypeptide and an active agent covalently attached to the polypeptide. Also provided is a method for protecting an active agent from degradation comprising covalently attaching the active agent to a polypeptide. Also provided is a method for controlling release of an active agent from a composition comprising covalently attaching the active agent to the polypeptide.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2002:186092 USPATFULL

TITLE: Active agent delivery systems and methods for protecting and administering active agents

INVENTOR(S): Piccariello, Thomas, Blacksburg, VA, UNITED STATES
Olon, Lawrence P., Bristol, TN, UNITED STATES
Kirk, Randal J., Radford, VA, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002099013	A1	20020725	
APPLICATION INFO.:	US 2001-933708	A1	20010822	(9)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2001-274622P	20010308	(60)
	US 2000-247621P	20001114	(60)
	US 2000-247620P	20001114	(60)
	US 2000-247595P	20001114	(60)
	US 2000-247594P	20001114	(60)
	US 2000-247635P	20001114	(60)
	US 2000-247634P	20001114	(60)
	US 2000-247606P	20001114	(60)
	US 2000-247607P	20001114	(60)
	US 2000-247608P	20001114	(60)
	US 2000-247609P	20001114	(60)
	US 2000-247610P	20001114	(60)
	US 2000-247611P	20001114	(60)
	US 2000-247702P	20001114	(60)
	US 2000-247701P	20001114	(60)
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	US 2000-247698P	20001114	(60)
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	US 2000-247833P	20001114	(60)
	US 2000-247832P	20001114	(60)
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	US 2000-247926P	20001114 (60)
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	US 2000-247929P	20001114 (60)
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	US 2000-247797P	20001114 (60)
	US 2000-247805P	20001114 (60)
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	US 2000-247802P	20001114 (60)
	US 2000-247801P	20001114 (60)
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	US 2000-247561P	20001114 (60)
	US 2000-247560P	20001114 (60)
	US 2000-247559P	20001114 (60)
	US 2000-247558P	20001114 (60)
	US 2000-247556P	20001114 (60)
	US 2000-247612P	20001114 (60)
	US 2000-247613P	20001114 (60)
	US 2000-247614P	20001114 (60)
	US 2000-247615P	20001114 (60)
	US 2000-247616P	20001114 (60)
	US 2000-247617P	20001114 (60)
	US 2000-247633P	20001114 (60)
	US 2000-247632P	20001114 (60)
	US 2000-247631P	20001114 (60)
	US 2000-247630P	20001114 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Robert M. Schulman, Esq., Hunton & Williams, Suite 1200, 1900 K Street, N.W., Washington, DC, 20006-1100
NUMBER OF CLAIMS: 40
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 8 Drawing Page(s)
LINE COUNT: 2048
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . pharmaceutically acceptable excipient. The microencapsulating agent can be selected from polyethylene glycol (PEG), an amino acid, a sugar and a **salt**. When an adjuvant is included in the composition, the adjuvant preferably activates an intestinal transporter.

DETD . . . the composition has the potential of stabilizing the polypeptide further. Stabilizers such as sugar, amino acids, polyethylene glycol (PEG) and **salts** have been shown to prevent protein unfolding. In another embodiment of the invention, a pre-first order release of the active agent is imparted by microencapsulating the carrier polypeptide-active agent conjugate in a polysaccharide, amino acid complex, PEG or **salts**.

DETD . . . pKb. Sodium acetate was the preferred reagent because its pKb is between that of sodium bromide, polyglutamic acid, and sodium **salt**. The reaction using basic alumina kept the T.sub.4-NCA and T.sub.3-NCA intact with no apparent capping or self-polymerization. The stability of. . .

DETD [0077] Experimentation with several weak bases revealed that a variety of sodium **salts** of a carboxylic acid work in capping polyglutamic acid. The reaction was tried with sodium propionate, sodium butyrate, and sodium. . .

DETD . . . splitting the reaction. The Mass range was determined from MALDI. The yield over 100% could reflect either the presence of **salts** or uneven distribution when the reaction mixture was split.

DETD . . . (360 MHz, CDCl.sub.3) .delta. 6.677 (d, 1H, naltrexone aromatic), 6.591 (d, 1H, naltrexone aromatic), 3.874 (s, 3H, methoxy group.), 0.6-0.5 **ppm** (m, 2H, naltrexone cyclopropyl) and 0.2-0.1 **ppm** (m, 2H, naltrexone cyclopropyl).

DETD . . . (d, 1H, naltrexone aromatic), 4.3-4.2 (m, 1H, glutamic acid .alpha.-proton), 1.7-1.3 (pair of bs, 18H, Boc and OtBu groups.), 0.6-0.4 **ppm** (m, 2H, naltrexone cyclopropyl) and 0.2-0.0 **ppm** (m, 2H, naltrexone cyclopropyl).

DETD . . . (d, 1H, naltrexone aromatic), 4.6-4.5 (m, 1H, aspartic acid .alpha.-proton), 1.6-1.3 (pair of bs, 18H, Boc and OtBu groups.), 0.7-0.5 **ppm** (m, 2H, naltrexone cyclopropyl) and 0.4-0.1 **ppm** (m, 2H, naltrexone cyclopropyl).

DETD . . . ml) was stirred at ambient temperatures for 2 hours. Solvent was removed to obtain glu(acetaminophen) (0.90 g) as the HCl **salt**: .sup.1H NMR (D.sub.2O) .delta. 2.19 (s, 3H, acetaminophen CH.sub.3), 2.41 (m, 2H, Glu-.beta. H), 2.97 (t, 2H, Glu-.gamma. H), 4.18. . .

DETD [0160] This material was dissolved in 1.5 ml dry anisole and stirred with 0.3 ml anhydrous **methanesulfonic acid** for 3 h upon which another 0.3 ml anhydrous **methanesulfonic acid** was added and the solution stirred for 1 h. The reaction mixture was poured into 6 ml Et.sub.2O and refrigerated. . .

DETD [0163] The protected polymer was dissolved in 1.5 ml dry anisole and stirred with 1.3 ml anhyd **methanesulfonic acid** for 4 h. The solution was concentrated to 0.5 ml by rotary evaporation. Et.sub.2O (8 ml) was added and the. . .

CLM What is claimed:

. . . said microencapsulating agent is selected from the group consisting of polyethylene glycol (PEG), an amino acid, a sugar and a **salt** .

IT 50-06-6, Phenobarbital, biological studies 50-18-0, Cyclophosphamide 50-35-1, Thalidomide 50-44-2, Mercaptopurine 50-78-2, Acetylsalicylic acid 50-81-7, Vitamin C, biological studies 51-21-8, Fluorouracil 51-61-6, Dopamine, biological studies 51-63-8, Dextroamphetamine sulfate 51-98-9, Norethindrone acetate 52-01-7, Spironolactone 52-24-4, Thiotepa 52-86-8, Haloperidol 53-36-1, Methylprednisolone Acetate 54-31-9, Furosemide 55-63-0, Nitroglycerin 57-63-6, Ethinyl estradiol 58-08-2, Caffeine, biological studies 58-18-4, Methyltestosterone 58-25-3, Chlordiazepoxide 58-33-3, Promethazine hydrochloride 58-55-9, Theophylline, biological studies 58-61-7, Adenosine, biological studies 58-93-5, Hydrochlorothiazide 59-42-7, Phenylephrine 60-54-8, Tetracycline 60-87-7, Promethazine 64-31-3, Morphine Sulfate 67-20-9, Nitrofurantoin 67-92-5, Dicyclomine hydrochloride 68-19-9, Vitamin B12 68-22-4, Norethindrone 71-58-9, Medroxyprogesterone acetate 71-68-1, Hydromorphone hydrochloride 74-79-3, Arginine, biological studies 76-41-5, Oxymorphone 76-42-6, Oxycodone 76-58-4, Ethylmorphine 78-44-4, Carisoprodol 84-02-6, Prochlorperazine maleate 87-08-1, Penicillin V 87-33-2, Isosorbide Dinitrate 89-57-6, Mesalamine 90-82-4, Pseudoephedrine 93-14-1, Guaifenesin 113-45-1, Methylphenidate 113-52-0 113-92-8, Chlorpheniramine maleate 114-07-8, Erythromycin 124-90-3, Oxycodone hydrochloride 125-28-0, Dihydrocodeine 125-29-1, Hydrocodone 125-33-7, Primidone 125-71-3, Dextromethorphan 128-13-2, Ursodiol

129-06-6, Warfarin Sodium 132-17-2, Benzatropine methanesulfonate
143-52-2, Methyldihydromorphinone 143-71-5, Hydrocodone bitartrate
152-11-4, Verapamil hydrochloride 297-76-7, Ethynodiol diacetate
298-46-4, Carbamazepine 298-59-9, Methylphenidate hydrochloride
303-49-1, Clomipramine 315-30-0, Allopurinol 318-98-9, Propranolol
Hydrochloride 378-44-9, Betamethasone 379-79-3, Ergotamine Tartrate
437-38-7, Fentanyl 439-14-5, Diazepam 446-86-6, Azathioprine
466-99-9, Hydromorphone 469-62-5, Propoxyphene 509-60-4,
Dihydromorphine 514-36-3, Fludrocortisone acetate 541-15-1,
Levocarnitine 549-18-8, Amitriptyline hydrochloride 554-13-2, Lithium
Carbonate 561-27-3, Diacetylmorphine 595-33-5, Megestrol acetate
604-75-1, Oxazepam 630-93-3, Sodium phenytoin 657-24-9, Metformin
745-65-3, Alprostadil 747-36-4, Hydroxychloroquine sulfate 797-63-7,
Levonorgestrel 846-49-1, Lorazepam 846-50-4, Temazepam 894-71-3,
Nortriptyline hydrochloride 959-24-0, Sotalol hydrochloride
1134-47-0, Baclofen 1403-66-3, Gentamicin 1404-93-9, Vancomycin
hydrochloride 1501-84-4, Rimantadine hydrochloride 1508-65-2,
Oxybutynin chloride 1622-61-3, Clonazepam 1665-48-1, Metaxalone
1744-22-5, Riluzole 1951-25-3, Amiodarone 2078-54-8, Propofol
2152-34-3, Pemoline 2375-03-3, Methylprednisolone sodium succinate
4205-91-8 4682-36-4, Orphenadrine citrate 4759-48-2, Isotretinoin
5786-21-0, Clozapine 6202-23-9, Cyclobenzaprine hydrochloride
6493-05-6, Pentoxifylline 6533-00-2, Norgestrel 7280-37-7,
Estropipate 7414-83-7, Etidronate disodium 9002-60-2,
Adrenocorticotrophic hormone, biological studies 9002-69-1, Relaxin
9005-49-6, Heparin, biological studies 9014-42-0, Thrombopoietin
9039-53-6, Urokinase 9041-08-1, Dalteparin sodium 9041-92-3,
..alpha..1-Protease inhibitor 9080-79-9, Sodium polystyrene sulfonate
10238-21-8, Glyburide 11005-12-2, .beta.-Phytosterol 11056-06-7,
Bleomycin 11140-85-5, Glucagon hydrochloride 13311-84-7, Flutamide
13614-98-7, Minocycline hydrochloride 14124-50-6, Hydrochlorothiazide-
triamterene mixt. 14611-52-0, Selegiline hydrochloride 14838-15-4,
Phenylpropanolamine 15307-79-6, Diclofenac sodium 15663-27-1,
Cisplatin 15686-71-2, Cephalexin 17140-78-2, Propoxyphene napsylate
17560-51-9, Metolazone 18559-94-9, Albuterol 19767-45-4, Mesna
20537-88-6, Amifostine 20830-75-5, Digoxin 21062-37-3D, analogs
21256-18-8, Oxaprozin 21829-25-4, Nifedipine 22071-15-4, Ketoprofen
23031-32-5, Terbutaline sulfate 25316-40-9, Doxorubicin hydrochloride
25322-68-3, Polyethylene glycol 25332-39-2, Trazodone hydrochloride
25614-03-3, Bromocriptine 26159-34-2, Naproxen sodium 26787-78-0,
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29354-16-3, Thyronine, iodo- 31677-93-7, Bupropion hydrochloride
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33069-62-4, Paclitaxel 33286-22-5, Diltiazem hydrochloride
33419-42-0, Etoposide 33564-30-6, Cefoxitin sodium 34552-83-5,
Loperamide hydrochloride 34580-13-7, Ketotifen 35189-28-7,
Norgestimate 36282-47-0, Tramadol hydrochloride 36505-84-7, Buspirone
36791-04-5, Ribavirin 37296-80-3, Colestipol hydrochloride
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Sparfosic acid 51481-61-9, Cimetidine 51773-92-3, Mefloquine
hydrochloride 52232-67-4, Teriparatide 53885-35-1, Ticlopidine
hydrochloride 53994-73-3, Cefaclor 54024-22-5, Desogestrel
54143-56-5, Flecainide acetate 54182-58-0, Sucralfate 54910-89-3,
Fluoxetine 54965-24-1, Tamoxifen citrate 55079-83-9, Acitretin

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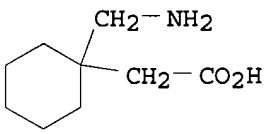
(compns. comprising a polypeptide and an active agent)

IT **60142-96-3**, Gabapentin
(compns. comprising a polypeptide and an active agent)

RN 60142-96-3 USPATFULL

CN Cyclohexaneacetic acid, 1-(aminomethyl)- (9CI) (CA INDEX NAME)

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L1             2 S E3-E4

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L4             9 S L3 AND PPM
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L7             2 S L6 AND PPM

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L8             7 L4 NOT L7

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L8 ANSWER 1 OF 7 USPATFULL on STN

AB A pharmaceutical composition containing substantially pure and stable gabapentin are disclosed wherein gabapentin has a pH of between 6.8 to 7.3.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2003:79181 USPATFULL

TITLE: Stable gabapentin having pH within a controlled range

INVENTOR(S): Singer, Claude, Kfar Saba, ISRAEL
Pilarski, Gideon, Holon, IL, UNITED STATES
Pesachovich, Michael, Givat Shmuel, ISRAEL

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003055109	A1	20030320
APPLICATION INFO.:	US 2002-227244	A1	20020826 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2001-880922, filed on 15 Jun 2001, ABANDONED

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-211966P	20000616 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: KENYON & KENYON, 1500 K STREET, N.W., SUITE 700, WASHINGTON, DC, 20005
NUMBER OF CLAIMS: 5
EXEMPLARY CLAIM: 1
LINE COUNT: 619

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . or less of corresponding lactam, (ii) not allowing the anion of a mineral acid in the composition to exceed 20 **ppm**, and (iii) using a specifically selected adjuvant that is not adverse to gabapentin stability.

SUMM . . . It has now been found that Augart's reliance on maintaining the anion of a mineral acid as not exceeding 20 **ppm** is misplaced. Thus, gabapentin and pharmaceutical formulations of gabapentin can be prepared and stored such that initially they do not. . .

SUMM [0010] The specific mineral acid disclosed by Augert is **hydrochloric acid** (column 3, lines 61-63; column 5, lines 24-29; exampes 1 and 2). The specification states, in particular

SUMM . . . for example, from the corresponding hydrochloride by ion exchange. The proportion of remaining hydrochloride admixtures should thereby not exceed 20 **ppm**.

SUMM [0013] 20 **ppm** of gabapentin hydrochloride corresponds to roughly 3 **ppm** of chloride ion, due to the higher molecular weight of gabapentin.

SUMM [0014] Augert's claims require gabapentin with "less than 20 **ppm** of the anion of a mineral acid", e.g. chloride.

SUMM [0018] As will be illustrated through exemplary embodiments 1-16, gabapentin may be prepared from the hydrochloride **salt** of gabapentin (gabapentin hydrochloride) and that in purified form gabapentin may have a pH in the range of 6.8-7.3, and preferably in the range of 7.0-7.2. The gabapentin formulation may also contain more than 20 **ppm** of chloride ion in the composition as measured by the amount of chloride ion in the composition.

SUMM . . . Exemplary embodiments 17-19 illustrate formulations of gabapentin containing varying amounts of chloride ion, some of which are

greater than 20 ppm and some less, and all of which initially contain less than 0.5% of lactam and after one year of storage. . .

DETD . . . chlorine anion content of the above-prepared gabapentin were obtained:

TABLE 1

Anion content and pH values after the reslurry in methanol

Run	Cl (ppm)	pH
A	4	6.94
B	20	7.01
C	<5	7.04
D	40	6.97
E	35	6.92
F	15	6.84

DETD . . . under vacuum resulting in pure gabapentin with a yield of 87%, pH of 7.15 and chlorine anion content of 50 ppm. Gabapentin so prepared initially contained less than 0.5% by weight of lactam, and, after a year of storage at 25.degree.. . .

DETD . . . under vacuum, resulting in pure gabapentin having a yield of 85%, pH of 6.8, and chlorine anion content of 50 ppm. Gabapentin so prepared contained less than 0.5% by weight of lactam, and, after a year of storage at 25.degree. C.. . .

DETD . . . reslurry as in Example 1B gabapentin pure was obtained at a yield of 58.8% and chloride anion content of 7 ppm Cl.sup.-.

DETD . . . reslurry as in Example 1B, gabapentin pure was obtained having a yield of 75.0% and chloride anion content of 213 ppm.

DETD . . . process, as in Example 1B, gabapentin pure was obtained having a yield of 68.0% and chloride anion content of 142 ppm.

DETD . . . After reslurry as in Example 1B, gabapentin pure was obtained having a yield of 67.8%, and anion content of 142 ppm.

DETD . . . After reslurry as in Example 1B, gabapentin pure was obtained, having a yield of 57.9%, and anion content of 142 ppm.

DETD . . . reslurry as in Example 1B, gabapentin pure was obtained having a yield of 57.9% and an anion content of 142 ppm.

DETD . . . values were obtained and tabulated in TABLE 2 as follows:

TABLE 2

Anion content and pH values for crystallization in methanol

Run	Cl (ppm)	pH
A	4	6.94
B	<5	7.2
C	150-200	6.9

DETD . . . under vacuum to give gabapentin pure having a yield of 81.4%, pH of 7.25 and chlorine anion content of 35 ppm.

DETD . . . under vacuum to give gabapentin pure at a yield of 81.4%, pH of 7.08 and anion content of Cl.sup.- 20 ppm.

DETD . . . under vacuum to give gabapentin pure having a yield of 72.4%, pH of 7.28 and anion (Cl.sup.-) content of 20 ppm.

DETD . . . under vacuum to give gabapentin pure having a yield of 75.8%, pH of 7.03 and anion content of (Cl.sup.-) 20 ppm.

DETD . . . under vacuum to give gabapentin pure having a yield of 77.6%, pH of 7.22 and anion (Cl.sup.-) content of 20 ppm.

DETD . . . vacuum to give gabapentin pure having a yield of 75%, pH of 7.17 and anion content (Cl.sup.-) of 10 **ppm**.

DETD [0072] The following gabapentin tablet formulation is prepared using gabapentin containing chloride ion ranging from 5 to 40 **ppm** and pH in the range of 6.84-7.04 according to Example 1. The following material is used:

Ingredients	Amounts

. . .

DETD [0076] Gabapentin of Example 2 (having chloride ion content of 50 **ppm** and pH of 7.15) is used to formulate tablets as in EXAMPLE 17, except that corn starch is replaced in. . .

DETD . . . gabapentin tablet of each sample is initially measured to have 0.5% by weight of a corresponding lactam, more than 50 **ppm** of chloride anion, and pH exceeding 6.8. The tablet is stored for one year at 25.degree. C. and 60% atmospheric. . .

DETD [0078] EXAMPLE 18 is repeated except that gabapentin of Example 4, having chloride ion of 7 **ppm** is used for formulating tablets. The resulting gabapentin tablet of each sample is initially measured to have 0.5% by weight of lactam and approximately 7 **ppm** of chloride anion. The tablet is stored for one year at 25.degree. C. and 60% atmospheric humidity and the increase. . .

DETD . . . show that, contrary to Augart's disclosure, the presence of anion of a mineral acid in an amount greater than 20 **ppm** does not adversely affect the stability of gabapentin when stored for one year at 5 25.degree. C. and 60% humidity. . .

CLM What is claimed is:
5. Gabapentin which contains less than 0.5% of the corresponding lactam, and less than 100 **ppm** of the anion of a mineral acid, which has a pH between 6.8 and 7.3, and which, after one year. . .

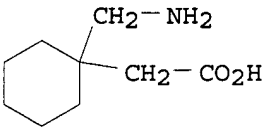
IT **60142-96-3P**, Gabapentin
(stable gabapentin having pH within a controlled range)

IT **60142-95-2**, Gabapentin hydrochloride
(stable gabapentin having pH within a controlled range)

IT **60142-96-3P**, Gabapentin
(stable gabapentin having pH within a controlled range)

RN 60142-96-3 USPATFULL

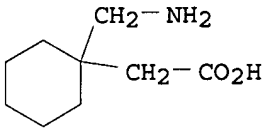
CN Cyclohexaneacetic acid, 1-(aminomethyl)- (9CI) (CA INDEX NAME)



IT **60142-95-2**, Gabapentin hydrochloride
(stable gabapentin having pH within a controlled range)

RN 60142-95-2 USPATFULL

CN Cyclohexaneacetic acid, 1-(aminomethyl)-, hydrochloride (9CI) (CA INDEX NAME)



● HCl

L8 ANSWER 2 OF 7 USPATFULL on STN
AB A process for the preparation of gabapentin of formula (I) ##STR1##

which comprises:

a) reduction of (1-nitromethyl-cyclohexyl)acetonitrile of formula (II) ##STR2##

to give 3-imino-2-aza-spiro[4.5]decan-2-ol of formula (III) ##STR3##

b) transformation of compound (III), by alkali treatment, into 2-hydroxy-2-aza-spiro[4.5]decan-3-one of formula (IV) ##STR4##

c) reduction of compound (IV) to give 2-aza-spiro[4.5]decan-3-one of ##STR5##

d) hydrolysis of compound (V) to gabapentin.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2003:11350 USPATFULL			
TITLE:	PROCESS FOR THE PREPARATION OF 1-AMINOMETHYL-1-CYCLOHEXANEACETIC ACID			
INVENTOR(S):	Velardi, Francesco, Cameri, ITALY Fornaroli, Mirco, Cameri, ITALY			
PATENT ASSIGNEE(S):	PROCOS S.P.A, CAMERI, ITALY (non-U.S. corporation)			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003009055	A1	20030109	
	US 6521788	B2	20030218	
APPLICATION INFO.:	US 2002-156059	A1	20020529	(10)
	NUMBER	DATE		
PRIORITY INFORMATION:	IT 2001-MI2001001132200010529			
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	APPLICATION			
LEGAL REPRESENTATIVE:	YOUNG & THOMPSON, 745 SOUTH 23RD STREET 2ND FLOOR, ARLINGTON, VA, 22202			
NUMBER OF CLAIMS:	7			
EXEMPLARY CLAIM:	1			
LINE COUNT:	233			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM [0004] Said patents disclose the hydrate hydrochloride **salt**, while gabapentin hydrate sodium **salt** is disclosed in U.S. Pat. No. 4,894,476.

10/024,339

SUMM . . . gabapentin ester and of the corresponding lactam (2-aza-spiro[4.5]decan-3-one), the acid hydrolysis of the latter and the treatment of the gabapentin **salt** with ion exchange resins.

DETD . . . is heated at 95.degree. C. for 10 hours, then cooled with ice-water and dropwise added with 43 ml of 30% **hydrochloric acid**. The mixture is stirred for 10' and added with 145 ml of water (exothermic reaction) and 110 ml of isopropyl. . .

DETD [0032] Proton spectrum in CD.sub.3OD (chemical shifts are expressed in **ppm** with tetramethylsilane as internal reference)

Chemical shifts	Multiplicity	Integration	Assignment
1.5-1.6	m	10 H	Cyclohexyl methylenes
2.23	s	2 H	methylene
3.4	s. . .		

DETD . . . g of water are refluxed for 1 hour, then cooled with stirring to precipitate a solid. 105 ml of conc. **hydrochloric acid** are dropped therein without exceeding 30.degree. C., checking pH which should be 1 or lower at the end of the. . .

DETD [0041] Proton spectrum in CD.sub.3OD (chemical shifts are expressed in **ppm** with tetramethylsilane as internal reference)

Chemical shifts	Multiplicity	Integration	Assignment
1.3-1.7	m	10 H	Cyclohexyl methylenes
2.55	s	2 H	methylene
3.55	s. . .		

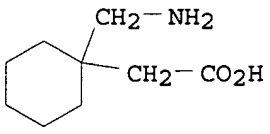
DETD [0047] 2 g (13 mmoles) of compound (V), 10 ml of water and 10 ml of conc. **hydrochloric acid** are refluxed for 4 hours. The mixture is cooled and washed twice with methylene chloride (10 ml each). The combined. . .

IT **60142-95-2P**, Gabapentin hydrochloride **60142-96-3P**, Gabapentin
(process for prepn. of gabapentin)

IT **60142-95-2P**, Gabapentin hydrochloride **60142-96-3P**, Gabapentin
(process for prepn. of gabapentin)

RN 60142-95-2 USPATFULL

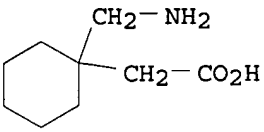
CN Cyclohexaneacetic acid, 1-(aminomethyl)-, hydrochloride (9CI) (CA INDEX NAME)



⊖ HCl

RN 60142-96-3 USPATFULL

CN Cyclohexaneacetic acid, 1-(aminomethyl)- (9CI) (CA INDEX NAME)



L8 ANSWER 3 OF 7 USPATFULL on STN

AB Pharmaceutical compositions containing substantially pure and stable gabapentin are disclosed wherein gabapentin contains an anion of a mineral acid, such as chloride, in amounts greater than 20 **ppm** .

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2002:119942 USPATFULL

TITLE: Stable gabapentin containing more than 20 **ppm** of chlorine ion

INVENTOR(S): Singer, Claude, Kfar Saba, ISRAEL
Pilarsky, Gideon, Holon, ISRAEL
Pesachovich, Michael, Givat Shmuel, ISRAEL

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002061931	A1	20020523	
	US 6531509	B2	20030311	
APPLICATION INFO.:	US 2001-880854	A1	20010615	(9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-211967P	20000616 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: KENYON & KENYON, 1500 K STREET, N.W., SUITE 700, WASHINGTON, DC, 20005
NUMBER OF CLAIMS: 7
EXEMPLARY CLAIM: 1
LINE COUNT: 623

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Stable gabapentin containing more than 20 **ppm** of chlorine ion

AB . . . gabapentin are disclosed wherein gabapentin contains an anion of a mineral acid, such as chloride, in amounts greater than 20 **ppm**.

SUMM . . . the present invention relates to a composition and a process for manufacturing pure and stable gabapentin having greater than 20 **ppm** of chloride ion.

SUMM . . . or less of corresponding lactam, (ii) not allowing the anion of a mineral acid in the composition to exceed 20 **ppm**, and (iii) using a specifically selected adjuvant that is not adverse to gabapentin stability.

SUMM . . . It has now been found that Augart's reliance on maintaining the anion of a mineral acid as not exceeding 20 **ppm** is misplaced. Thus, gabapentin and pharmaceutical formulations of gabapentin can be prepared and stored such that initially they do not. . .

SUMM [0010] The specific mineral acid disclosed by Augert is **hydrochloric acid** (column 3, lines 61-63; column 5, lines 24-29; exampes 1 and 2). The specification states, in particular

SUMM [0012] The proportion of remaining hydrochloride admixtures should thereby not exceed 20 **ppm**.

SUMM [0014] 20 **ppm** of gabapentin hydrochloride corresponds to roughly 3 **ppm** of chloride ion, due to the higher molecular weight of gabapentin.

SUMM [0015] Augert's claims require gabapentin with "less than 20 **ppm** of the anion of a mineral acid", e.g. chloride.

SUMM . . . Accordingly, the present invention relates to a pharmaceutical composition containing a pharmaceutically effective amount of gabapentin containing more than 20 **ppm** of an anion of a mineral acid and which initially contains less than 0.5% of a corresponding lactam and after. . .

SUMM . . . The present invention also relates to a process for preparing a stable pharmaceutical formulation containing gabapentin with more than 20 **ppm** of the anion of a mineral acid and which initially contains less than 0.5% of a corresponding lactam and after. . .

SUMM [0019] As will be illustrated through exemplary embodiments 1-16, gabapentin may be prepared from the hydrochloride **salt** of gabapentin (gabapentin hydrochloride) and that in purified form gabapentin may contain more than 20 **ppm** of chloride ion in the composition as measured by the amount of chloride ion in the composition.

SUMM . . . Exemplary embodiments 17-19 illustrate formulations of gabapentin containing varying amounts of chloride ion, some of which are greater than 20 **ppm** and some less, and all of which initially contain less than 0.5% of lactam and after one year of storage. . .

DETD . . . anion content of the above-prepared gabapentin were obtained:

TABLE 1

Anion content and pH values after the reslurry in methanol

Run	Cl (**ppm**)	pH
A	4	6.94
B	20	7.01
C	<5	7.04
D	40	6.97
E	35	6.92
F	15	6.84

DETD . . . under vacuum resulting in pure gabapentin with a yield of 87%, pH of 7.15 and chlorine anion content of 50 **ppm**. Gabapentin so prepared contains less than 0.5% by weight of lactam, and, after a year of storage at 25.degree. C.. . .

DETD . . . under vacuum, resulting in pure gabapentin having a yield of 85%, pH of 6.8, and chlorine anion content of 50 **ppm**. Gabapentin so prepared contained less than 0.5% by weight of lactam, and, after a year of storage at 25.degree. C.. . .

DETD . . . reslurry as in Example 1B gabapentin pure was obtained at a yield of 58.8% and chloride anion content of 7 **ppm** Cl.sup.-.

DETD . . . reslurry as in Example 1B, gabapentin pure was obtained having a yield of 75.0% and chloride anion content of 213 **ppm**.

DETD . . . process, as in Example 1B, gabapentin pure was obtained having a yield of 68.0% and chloride anion content of 142 **ppm**.

DETD . . . After reslurry as in Example 1B, gabapentin pure was obtained having a yield of 67.8%, and anion content of 142 **ppm**.

DETD . . . After reslurry as in Example 1B, gabapentin pure was obtained, having a yield of 57.9%, and anion content of 142 **ppm**.

DETD . . . reslurry as in Example 1B, gabapentin pure was obtained having

a yield of 57.9% and an anion content of 142 **ppm**.

DETD . . . values were obtained and tabulated in TABLE 2 as follows:

TABLE 2

Anion content and PH values for crystallization in methanol

Run	Cl (**ppm**)	pH
A	4	6.94
B	<5	72
C	150-200	6.9

DETD [0058] 35 **ppm**.

DETD . . . under vacuum to give gabapentin pure at a yield of 81.4%, pH of 7.08 and anion content of Cl.sup.- 20 **ppm**.

DETD . . . under vacuum to give gabapentin pure having a yield of 72.4%, pH of 7.28 and anion (Cl.sup.-) content of 20 **ppm**.

DETD . . . under vacuum to give gabapentin pure having a yield of 75.8%, pH of 7.03 and anion content of (Cl.sup.-) 20 **ppm**.

DETD . . . under vacuum to give gabapentin pure having a yield of 77.6%, pH of 7.22 and anion (Cl.sup.-) content of 20 **ppm**.

DETD . . . under vacuum to give gabapentin pure having a yield of 75%, pH of 7.17 and anion content (Cl.sup.-) of 10 **ppm**.

DETD [0073] The following gabapentin tablet formulation is prepared using gabapentin containing chloride ion ranging from 5 to 40 **ppm** and pH in the range of 6.84-7.04 according to Example 1. The following material is used:

Ingredients	Amounts

. . .

DETD [0076] Gabapentin of Example 2 (having chloride ion content of 50 **ppm** and pH of 7.15) is used to formulate tablets as in EXAMPLE 17, except that corn starch is replaced in. . .

DETD . . . gabapentin tablet of each sample is initially measured to have 0.5% by weight of a corresponding lactam, more than 50 **ppm** of chloride anion, and pH exceeding 6.8. The tablet is stored for one year at 25.degree. C. and 60% atmospheric. . .

DETD [0078] EXAMPLE 18 is repeated except that gabapentin of Example 4, having chloride ion of 7 **ppm** is used for formulating tablets. The resulting gabapentin tablet of each sample is initially measured to have 0.5% by weight of lactam and approximately 7 **ppm** of chloride anion. The tablet is stored for one year at 55.degree. C. and 50% atmospheric humidity and the increase. . .

DETD . . . show that, contrary to Augart's disclosure, the presence of anion of a mineral acid in an amount greater than 20 **ppm** does not adversely affect the stability of gabapentin when stored for one year at 25.degree. C. and 60% humidity. The. . .

CLM What is claimed is:

. . . composition comprising gabapentin and initially containing less than 0.5% by weight of a corresponding lactam and having greater than 20 **ppm** of an anion of a mineral acid, which, after one year of storage at 25.degree. C. and 60% humidity the. . .

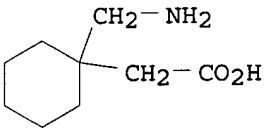
. . . The pharmaceutical composition of claim 1, wherein the amount of said anion of a mineral acid does not exceed 100 **ppm**.

7. Gabapentin which contains less than 0.5% of the corresponding lactam and between 20 and 100 **ppm** of the anion of a mineral acid and which, after one year of storage at 25.degree. C. and 60% humidity. . . . . least one adjuvant, and initially containing less than 0.5% by weight of a corresponding lactam and having greater than 20 **ppm** of chloride, which, after one year of storage at 25.degree. C. and 60% humidity the conversion of gabapentin to its. . .

IT 63-42-3, Lactose 79-41-4D, Methacrylic acid, esters, polymers 5415-98-5D, polymers with methacrylates 7631-86-9, Silica, biological studies 9003-39-8, PVP 9004-65-3, HPMC 9005-25-8, Starch, biological studies 9063-38-1, Sodium starch glycolate 12619-70-4, Cyclodextrin 13463-67-7, Titanium oxide, biological studies 14807-96-6, Talc, biological studies 16887-00-6, Chloride, biological studies **60142-95-2**, Gabapentin hydrochloride **60142-96-3**, Gabapentin 74811-65-7, Sodium croscarmellose 77538-19-3, Glyceryl behenate 106392-12-5, Poloxamer
(stable gabapentin contg. more than 20 ppm chloride)

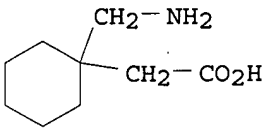
IT **60142-95-2**, Gabapentin hydrochloride **60142-96-3**, Gabapentin
(stable gabapentin contg. more than 20 ppm chloride)

RN 60142-95-2 USPATFULL
CN Cyclohexaneacetic acid, 1-(aminomethyl)-, hydrochloride (9CI) (CA INDEX NAME)



● HCl

RN 60142-96-3 USPATFULL
CN Cyclohexaneacetic acid, 1-(aminomethyl)- (9CI) (CA INDEX NAME)



L8 ANSWER 4 OF 7 USPATFULL on STN
AB A pharmaceutical composition containing substantially pure and stable gabapentin are disclosed wherein gabapentin has a pH of between 6.8 to 7.3.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2002:85616 USPATFULL
TITLE: Stable gabapentin having pH within a controlled range
INVENTOR(S): Singer, Claude, Kfar Saba, ISRAEL

Pilarski, Gideon, Holon, ISRAEL
Pesachovich, Michael, Givat Shmuel, ISRAEL

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002045662	A1	20020418
APPLICATION INFO.:	US 2001-880922	A1	20010615 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-211966P	20000616 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: KENYON & KENYON, 1500 K STREET, N.W., SUITE 700, WASHINGTON, DC, 20005
NUMBER OF CLAIMS: 5
EXEMPLARY CLAIM: 1
LINE COUNT: 622
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . or less of corresponding lactam, (ii) not allowing the anion of a mineral acid in the composition to exceed 20 **ppm**, and (iii) using a specifically selected adjuvant that is not adverse to gabapentin stability.

SUMM . . . It has now been found that Augart's reliance on maintaining the anion of a mineral acid as not exceeding 20 **ppm** is misplaced. Thus, gabapentin and pharmaceutical formulations of gabapentin can be prepared and stored such that initially they do not. . .

SUMM [0012] The specific mineral acid disclosed by Augert is **hydrochloric acid** (column 3, lines 61-63; column 5, lines 24-29; exampes 1 and 2). The specification states, in particular

SUMM . . . for example, from the corresponding hydrochloride by ion exchange. The proportion of remaining hydrochloride admixtures should thereby not exceed 20 **ppm**.

SUMM [0015] 20 **ppm** of gabapentin hydrochloride corresponds to roughly 3 **ppm** of chloride ion, due to the higher molecular weight of gabapentin.

SUMM [0016] Augert's claims require gabapentin with "less than 20 **ppm** of the anion of a mineral acid", e.g. chloride.

SUMM [0020] As will be illustrated through exemplary embodiments 1-16, gabapentin may be prepared from the hydrochloride **salt** of gabapentin (gabapentin hydrochloride) and that in purified form gabapentin may have a pH in the range of 6.8-7.3, and preferably in the range of 7.0-7.2. The gabapentin formulation may also contain more than 20 **ppm** of chloride ion in the composition as measured by the amount of chloride ion in the composition.

SUMM . . . Exemplary embodiments 17-19 illustrate formulations of gabapentin containing varying amounts of chloride ion, some of which are greater than 20 **ppm** and some less, and all of which initially contain less than 0.5% of lactam and after one year of storage. . .

DETD . . . chlorine anion content of the above-prepared gabapentin were obtained:

TABLE 1

Anion content and PH values after the reslurry in methanol

Run	Cl.sup.-(**ppm**)	pH
A	4	6.94

B	20	7.01
C	<5	7.04
D	40	6.97
E	35	6.92
F	15	6.84

DETD . . . under vacuum resulting in pure gabapentin with a yield of 87%, pH of 7.15 and chlorine anion content of 50 **ppm**. Gabapentin so prepared initially contained less than 0.5% by weight of lactam, and, after a year of storage at 25.degree.. . .

DETD . . . under vacuum, resulting in pure gabapentin having a yield of 85%, pH of 6.8, and chlorine anion content of 50 **ppm**. Gabapentin so prepared contained less than 0.5% by weight of lactam, and, after a year of storage at 25.degree. C.. . .

DETD . . . reslurry as in Example 1B gabapentin pure was obtained at a yield of 58.8% and chloride anion content of 7 **ppm** Cl.sup.-.

DETD . . . reslurry as in Example 1B, gabapentin pure was obtained having a yield of 75.0% and chloride anion content of 213 **ppm**.

DETD . . . process, as in Example 1B, gabapentin pure was obtained having a yield of 68.0% and chloride anion content of 142 **ppm**.

DETD . . . After reslurry as in Example 1B, gabapentin pure was obtained having a yield of 67.8%, and anion content of 142 **ppm**.

DETD . . . After reslurry as in Example 1B, gabapentin pure was obtained, having a yield of 57.9%, and anion content of 142 **ppm**.

DETD . . . reslurry as in Example 1B, gabapentin pure was obtained having a yield of 57.9% and an anion content of 142 **ppm**.

DETD . . . values were obtained and tabulated in TABLE 2 as follows:

TABLE 2

Anion content and PH values for crystallization in methanol

Run	Cl (**ppm**)	pH
A	4	6.94
B	<5	7.2
C	150-200	6.9

DETD . . . under vacuum to give gabapentin pure having a yield of 81.4%, pH of 7.25 and chlorine anion content of 35 **ppm**.

DETD . . . under vacuum to give gabapentin pure at a yield of 81.4%, pH of 7.08 and anion content of Cl.sup.- 20 **ppm**.

DETD . . . under vacuum to give gabapentin pure having a yield of 72.4%, pH of 7.28 and anion (Cl.sup.-) content of 20 **ppm**.

DETD . . . under vacuum to give gabapentin pure having a yield of 75.8%, pH of 7.03 and anion content of (Cl.sup.-) 20 **ppm**.

DETD . . . under vacuum to give gabapentin pure having a yield of 77.6%, pH of 7.22 and anion (Cl.sup.-) content of 20 **ppm**.

DETD . . . under vacuum to give gabapentin pure having a yield of 75%, pH of 7.17 and anion content (Cl.sup.-) of 10 **ppm**.

DETD [0077] The following gabapentin tablet formulation is prepared using gabapentin containing chloride ion ranging from 5 to 40 **ppm** and pH in the range of 6.84-7.04 according to Example 1. The following material is used:

Ingredients	Amounts

. . .

DETD [0080] Gabapentin of Example 2 (having chloride ion content of 50 **ppm** and pH of 7.15) is used to formulate tablets as in EXAMPLE 17, except that corn starch is replaced in. . .

DETD . . . gabapentin tablet of each sample is initially measured to have 0.5% by weight of a corresponding lactam, more than 50 **ppm** of chloride anion, and pH exceeding 6.8. The tablet is stored for one year at 25.degree. C. and 60% atmospheric. . .

DETD [0082] EXAMPLE 18 is repeated except that gabapentin of Example 4, having chloride ion of 7 **ppm** is used for formulating tablets. The resulting gabapentin tablet of each sample is initially measured to have 0.5% by weight of lactam and approximately 7 **ppm** of chloride anion. The tablet is stored for one year at 25.degree. C. and 60% atmospheric humidity and the increase. . .

DETD . . . show that, contrary to Augart's disclosure, the presence of anion of a mineral acid in an amount greater than 20 **ppm** does not adversely affect the stability of gabapentin when stored for one year at 25.degree. C. and 60% humidity (or. . .

CLM What is claimed is:
5. Gabapentin which contains less than 0.5% of the corresponding lactam, and less than 100 **ppm** of the anion of a mineral acid, which has a pH between 6.8 and 7.3, and which, after one year. . .

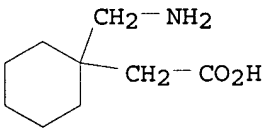
IT **60142-96-3P**, Gabapentin
(stable gabapentin having pH within a controlled range)

IT **60142-95-2**, Gabapentin hydrochloride
(stable gabapentin having pH within a controlled range)

IT **60142-96-3P**, Gabapentin
(stable gabapentin having pH within a controlled range)

RN 60142-96-3 USPATFULL

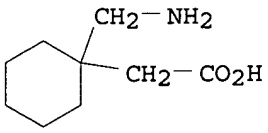
CN Cyclohexaneacetic acid, 1-(aminomethyl)- (9CI) (CA INDEX NAME)



IT **60142-95-2**, Gabapentin hydrochloride
(stable gabapentin having pH within a controlled range)

RN 60142-95-2 USPATFULL

CN Cyclohexaneacetic acid, 1-(aminomethyl)-, hydrochloride (9CI) (CA INDEX NAME)



L8 ANSWER 5 OF 7 USPATFULL on STN

Delacroix

AB The present invention concerns cyclic amino acids of formula ##STR1## substantially free from the lactam ##STR2## wherein n is an integer of from 4 to 6, a process for the preparation thereof, compositions containing the compounds and methods of using them.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2000:50732 USPATFULL
TITLE: Lactam-free amino acids
INVENTOR(S): Augart, Helmut, Waldkirch, Germany, Federal Republic of
Gebhardt, Uwe, Waldkirch, Germany, Federal Republic of
Herrmann, Wolfgang, Merzhausen, Germany, Federal Republic of
PATENT ASSIGNEE(S): Godecke Aktiengesellschaft, Berlin, Germany, Federal Republic of (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6054482		20000425
APPLICATION INFO.:	US 1995-377618		19950125 (8)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1993-20270, filed on 18 Feb 1993, now abandoned which is a continuation of Ser. No. US 1992-865723, filed on 8 Apr 1992, now abandoned which is a continuation of Ser. No. US 1990-570500, filed on 21 Aug 1990, now abandoned

	NUMBER	DATE
PRIORITY INFORMATION:	DE 1989-3928183	19890825

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Shippen, Michael L.
LEGAL REPRESENTATIVE: Tinney, Francis J.
NUMBER OF CLAIMS: 11
EXEMPLARY CLAIM: 1,7
LINE COUNT: 301

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . and cranial traumas. U.S. Pat. Nos. 4,024,175 and 4,087,544 cover the compound and its uses. They also disclose an acid **salt**, i.e., gabapentin hydrochloride hydrate, in a ratio of 4:4:1 and a sodium **salt** of gabapentin hydrate in a ratio of 2:1.

SUMM . . . is a hydrogen atom or a lower alkyl radical and n is 4, 5, or 6 and the pharmaceutically acceptable **salts** thereof, which depend upon known methods used for the preparation of primary amines or amino acid.

SUMM The instant invention covers a compound of formula ##STR5## or a pharmaceutically acceptable **salt** thereof substantially free from ##STR6## wherein n is an integer of from 4 to 6.

SUMM (c) converting the product of step (b) to a pharmaceutically acceptable **salt** thereof, if desired.

SUMM A preferred process of the instant invention is one wherein the mineral **acid hydrochloric acid** is used and an ion exchanger is used for anion removal.

SUMM . . . hydrogen atom or lower alkyl and n is an integer 4, 5 or 6, as well as the pharmacologically acceptable **salts** thereof. These compounds possess valuable pharmacodynamic properties. The compounds of formula (I) have an extraordinarily low toxicity. In animal experiments,. . .

SUMM . . . converted by esterification into a lower alkyl ester or by

reaction with an acid or base into a pharmacologically acceptable **salt**.

SUMM The hydrochloride of gabapentin was the most suitable form of the active material since **salts** and especially hydrochlorides as a rule usually provide especially good stability and good solubility. However, in some cases, pharmaceutical compositions. . .

SUMM . . . for example, from the corresponding hydrochloride by ion exchange. The proportion of remaining hydrochloride admixtures should thereby not exceed 20 **ppm**. The same also applies to other mineral acids.

DETD 22.3 L of water and 22.3 L of concentrated **hydrochloric acid** are mixed in a T100 reactor and 6.41 kg gabapentin lactam added while stirring. The clear brown solution formed is. . .

CLM What is claimed is:

. . . 0.5% by weight of a compound of Formula VIII ##STR18## wherein n is as defined above and less than 20 **ppm** of an anion of a mineral acid comprising: (a) hydrolysis of a compound of Formula VII containing a compound of. . . VIII alone with a mixture of equal volumes of a concentrated mineral acid and water to afford an acid addition **salt** of a compound of Formula VII and (b) converting the acid addition **salt** of a compound of Formula VII by ion exchange to a compound of Formula VII containing less than 0.5% by weight of a compound of Formula VIII and less than 20 **ppm** of an anion of a mineral acid.

2. A process according to claim 1, wherein in step (a) the **acid** is **hydrochloric acid**.

3. A process for preparing stable and pure pharmaceutical compositions containing a compound of formula (VII) ##STR19## wherein n is. . . VIII alone with a mixture of equal volumes of a concentrated mineral acid and water to afford an acid addition **salt** of a compound of formula VII substantially free of a compound of formula VIII, (b) converting the acid addition **salt** of a compound of formula VII by ion exchange to a compound of formula VII containing less than 0.5% by. . . of a compound of formula VIII, wherein the proportion of remaining anion of a mineral acid does not exceed 20 **ppm**, (c) adding pharmaceutically acceptable adjuvants to form a pharmaceutical composition wherein the adjuvants do not promote the formation of a. . .

5. A process of claim 3, wherein the mineral **acid** is **hydrochloric acid**.

7. A stable and pure pharmaceutical composition in unit dry medicinal dosage form consisting essentially of: (i) an active ingredient. . . free amino acid, crystalline anhydrous form containing less than 0.5% by weight of its corresponding lactam and less than 20 **ppm** of an anion of a mineral acid and (ii) one or more pharmaceutically acceptable adjuvants that do not promote conversion. . .

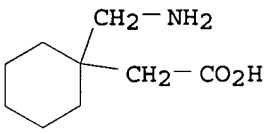
11. A pharmaceutical composition according to claim 7,wherein in (i) the mineral **acid** is **hydrochloric acid**.

IT **60142-95-2P**
(prepn. and conversion of, to free base)

IT **60142-96-3P**
(prepn. of, from gabapentin lactam)

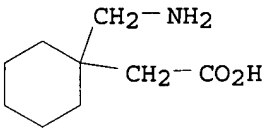
IT **60142-95-2P**
(prepn. and conversion of, to free base)

RN 60142-95-2 USPATFULL
CN Cyclohexaneacetic acid, 1-(aminomethyl)-, hydrochloride (9CI) (CA INDEX NAME)



● HCl

IT **60142-96-3P**
(prepn. of, from gabapentin lactam)
RN 60142-96-3 USPATFULL
CN Cyclohexaneacetic acid, 1-(aminomethyl)- (9CI) (CA INDEX NAME)



L8 ANSWER 6 OF 7 USPATFULL on STN
AB A novel crystalline form of gabapentin and a novel processes for the small and large scale preparations of the anticonvulsant compound in a highly pure state is disclosed. This novel hydrate is produced by a cost effective process which provides an additional purification stage.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	90:76869 USPATFULL
TITLE:	Gabapentin mohohydrate and a process for producing the same
INVENTOR(S):	Butler, Donald E., Holland, MI, United States Greenman, Barbara J., Door, MI, United States
PATENT ASSIGNEE(S):	Warner-Lambert Company, Morris Plains, NJ, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4960931		19901002
APPLICATION INFO.:	US 1989-417995		19891006 (7)
RELATED APPLN. INFO.:	Division of Ser. No. US 1988-188819, filed on 2 May 1988, now patented, Pat. No. US 4894476		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Shippen, Michael L.		
LEGAL REPRESENTATIVE:	Anderson, Elizabeth M.		
NUMBER OF CLAIMS:	7		
EXEMPLARY CLAIM:	1,7		
LINE COUNT:	295		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . and cranial traumas. U.S. Pat. Nos. 4,024,175 and 4,087,544 cover the compound and its uses. They also disclose an acid **salt** , i.e. gabapentin.hydrochloride hydrate in a ratio of 4:4:1 and a sodium **salt** of gabapentin hydrate in a ratio of 2:1. These patents are hereby incorporated by reference.

SUMM . . . is a hydrogen atom or a lower alkyl radical and n is 4, 5, or 6 and the pharmaceutically acceptable **salts** thereof, which depend upon known methods used for the preparation of primary amines or amino acids.

SUMM . . . into the desired (1-aminomethyl)-1-cyclohexaneacetic acid by acidic hydrolysis (preferred) to give an acid or basic hydrolysis to give a basic **salt** or followed by acidification to give an acid **salt**.

SUMM (a) pouring a 1 N solution of an acid **salt** of (1-aminomethyl)-cyclohexaneacetic acid onto an ion exchange column in the basic form and eluting that column with deionized water;

SUMM Useful acid **salts** are hydrobromide, sulphate, methane sulfonate, hydrochloride and the like. The preferred acid **salt** in step (a) is the hydrochloride.

SUMM (a) pouring a solution of an acid **salt** of (1-aminomethyl)-cyclohexaneacetic acid in deionized water onto an ion exchange column in the basic form and eluting the column with. . .

SUMM Useful acid **salts** include but are not limited to hydrobromide, sulphate, methanesulfonate, hydrochloride and the like. The preferred **salt** is the hydrochloride and in a preferred ratio is 4:4:1.

SUMM The preferred acid **salt** of (1-aminomethyl)-cyclohexaneacetic acid is the monohydrochloride hydrate in a ratio of 4:4:1.

SUMM . . . of this kind include, for example, tartrate and citrate buffers, ethanol, complex-forming agents (such as ethylenediamine-tetraacetic acid and the nontoxic **salts** thereof), as well as high molecular weight polymers (such as liquid polyethylene oxide) for viscosity regulation. Solid carrier materials include,. . .

DETD CL.sup.- : 8.6 **ppm**

DETD . . . The resin is treated with 3700 L of filtered deionized water that has been mixed with 60.6 Kg of concentrated **hydrochloric acid**. The **acid** treatment is repeated with fresh acid. The resin is washed with 6400 L of filtered deionized water. The resin is. . .

DETD The resin is treated with 3700 L of filtered deionized water that has been mixed with 60.6 Kg of concentrated **hydrochloric acid**. The **acid** treatment is repeated with fresh acid. The resin is washed with 6400 L of filtered deionized water. The resin is. . .

DETD The resin is treated with 3700 L of filtered deionized water that has been mixed with 60.6 Kg of concentrated **hydrochloric acid**. The **acid** treatment is repeated with fresh acid. The resin is washed with 6400 L of filtered deionized water. The resin is. . .

DETD CL.sup.- : 30 **ppm**

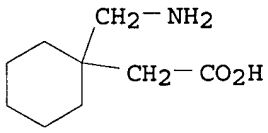
DETD CL.sup.- : 22 **ppm**

CLM What is claimed is:

. . . . A process for the preparation of a compound of formula ##STR6## which comprises: (a) pouring a solution of an acid **salt** of (1-aminomethyl)-cyclohexaneacetic acid in deionized water onto an ion exchange column in the basic form and eluting the column with. . .

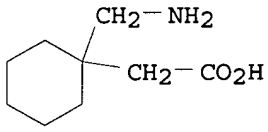
2. A process according to claim 1 wherein in step (a) the acid **salt** is gabapentin hydrochloride hydrate (4:4:1).

IT **60142-95-2**, Gabapentin hydrochloride
(gabapentin monohydrate from, pure)
IT **60142-96-3P**
(prepn. of highly pure)
IT **60142-95-2**, Gabapentin hydrochloride
(gabapentin monohydrate from, pure)
RN 60142-95-2 USPATFULL
CN Cyclohexaneacetic acid, 1-(aminomethyl)-, hydrochloride (9CI) (CA INDEX NAME)



● HCl

IT **60142-96-3P**
(prepn. of highly pure)
RN 60142-96-3 USPATFULL
CN Cyclohexaneacetic acid, 1-(aminomethyl)- (9CI) (CA INDEX NAME)



L8 ANSWER 7 OF 7 USPATFULL on STN
AB A novel crystalline form of gabapentin and a novel processes for the small and large scale preparations of the anticonvulsant compound in a highly pure state is disclosed. This novel hydrate is produced by a cost effective process which provides an additional purification stage.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	90:4484 USPATFULL		
TITLE:	Gabapentin monohydrate and a process for producing the same		
INVENTOR(S):	Butler, Donald E., Holland, MI, United States Greenman, Barbara J., Door, MI, United States		
PATENT ASSIGNEE(S):	Warner-Lambert Company, Morris Plains, NJ, United States (U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4894476		19900116
APPLICATION INFO.:	US 1988-188819		19880502 (7)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		

PRIMARY EXAMINER: Shippen, Michael L.
LEGAL REPRESENTATIVE: Anderson, Elizabeth M.
NUMBER OF CLAIMS: 2
EXEMPLARY CLAIM: 1
LINE COUNT: 271
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . and cranial traumas. U.S. Pat. Nos. 4,024,175 and 4,087,544 cover the compound and its uses. They also disclose an acid **salt**, i.e. gabapentin.hydrochloride hydrate in a ratio of 4:4:1 and a sodium **salt** of gabapentin hydrate in a ratio of 2:1. These patents are hereby incorporated by reference.

SUMM . . . is a hydrogen atom or a lower alkyl radical and n is 4, 5, or 6 and the pharmaceutically acceptable **salts** thereof, which depend upon known methods used for the preparation of primary amines or amino acids.

SUMM . . . into the desired (1-aminomethyl)-1-cyclohexaneacetic acid by acidic hydrolysis (preferred) to give an acid or basic hydrolysis to give a basic **salt** or followed by acidification to give an acid **salt**.

SUMM . . . is for the preparation of a compound of formula ##STR3## which comprises: (a) pouring a 1N solution of an acid **salt** of (1-aminomethyl)-cyclohexaneacetic acid onto an ion exchange column in the basic form and eluting that column with deionized water;

SUMM Useful acid **salts** are hydrobromide, sulphate, methane sulfonate, hydrochloride and the like. The preferred acid **salt** in step (a) is the hydrochloride.

SUMM A process for the preparation of a compound of formula ##STR4## which comprises: (a) pouring a solution of an acid **salt** of (1-aminomethyl)-cyclohexaneacetic acid in deionized water onto an ion exchange column in the basic form and eluting the column with. . .

SUMM Useful acid **salts** include but are not limited to hydrobromide, sulphate, methanesulfonate, hydrochloride and the like. The preferred **salt** is the hydrochloride and in a preferred ratio is 4:4:1.

SUMM The preferred acid **salt** of (1-aminomethyl)-cyclohexaneacetic acid is the monohydrochloride hydrate in a ratio of 4:4:1.

SUMM . . . of this kind include, for example, tartrate and citrate buffers, ethanol, complex-forming agents (such as ethylenediaminetetraacetic acid and the nontoxic **salts** thereof), as well as high molecular weight polymers (such as liquid polyethylene oxide) for viscosity regulation. Solid carrier materials include,. . .

DETD Analytical data: HPLC: 89.27% w/w against dry analytical standard, H.sub.2 O: 9.68%.+-.0.5, mp 156.degree.-156.7.degree. C. (dec), CL.sup.-: 8.6 **ppm**.

DETD . . . The resin is treated with 3700 L of filtered deionized water that has been mixed with 60.6 Kg of concentrated **hydrochloric acid**. The **acid** treatment is repeated with fresh acid. The resin is washed with 6400 L of filtered deionized water. The resin is. . .

DETD The resin is treated with 3700 L of filtered deionized water that has been mixed with 60.6 Kg of concentrated **hydrochloric acid**. The **acid** treatment is repeated with fresh acid. The resin is washed with 6400 L of filtered deionized water. The resin is. . .

DETD The resin is treated with 3700 L of filtered deionized water that has been mixed with 60.6 Kg of concentrated **hydrochloric acid**. The **acid** treatment is repeated with fresh acid. The resin is washed with 6400 L of filtered deionized water. The resin is. . .

DETD . . . data: HPLC: 89.4 w/w against dry reference standard, H.sub.2 O (Karl Fischer): 9.69%.+-.0.5, mp 156.degree.-156.7.degree. C. (dec), CL.sup.- : 30 **ppm**.

DETD . . . data: HPLC: 100.6% w/w against dry analytical standard, H.sub.2 O: 0.09%. CH.sub.3 OH: 0.01%, (CH.sub.3).sub.2 CHOH: 0.01%, CL.sup.- : 22 **ppm**, Melting point: 161.7.degree.-162.6.degree. C. (dec.).

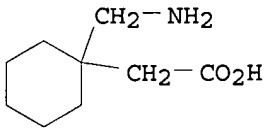
IT **60142-95-2**, Gabapentin hydrochloride
(gabapentin monohydrate from, pure)

IT **60142-96-3P**
(prepn. of highly pure)

IT **60142-95-2**, Gabapentin hydrochloride
(gabapentin monohydrate from, pure)

RN 60142-95-2 USPATFULL

CN Cyclohexaneacetic acid, 1-(aminomethyl)-, hydrochloride (9CI) (CA INDEX NAME)

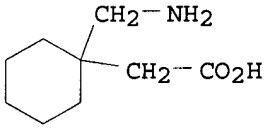


● HCl

IT **60142-96-3P**
(prepn. of highly pure)

RN 60142-96-3 USPATFULL

CN Cyclohexaneacetic acid, 1-(aminomethyl)- (9CI) (CA INDEX NAME)



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FILE 'REGISTRY' ENTERED AT 20:11:08 ON 24 OCT 2003
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STRUCTURE FILE UPDATES:   23 OCT 2003  HIGHEST RN 608489-22-1
DICTIONARY FILE UPDATES:  23 OCT 2003  HIGHEST RN 608489-22-1

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2003

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available.  See HELP
PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> e gabapentin/cn
E1            1     GABALLON/CN
E2            1     GABAMIDE HYDROCHLORIDE/CN
E3            1 --> GABAPENTIN/CN
E4            1     GABAPENTIN HYDROCHLORIDE/CN
E5            1     GABAPENTIN-LACTAM/CN
E6            1     GABARAP (HUMAN)/CN
E7            1     GABASE/CN
E8            1     GABATRIL/CN
E9            1     GABAZINE/CN
E10           1     GABBROCLAR/CN
E11           1     GABBROCOL/CN
E12           1     GABBROMICINA/CN

=> s e3-e4
              1 GABAPENTIN/CN
              1 "GABAPENTIN HYDROCHLORIDE"/CN
L1            2 (GABAPENTIN/CN OR "GABAPENTIN HYDROCHLORIDE"/CN)

=> d l1 1 2

L1   ANSWER 1 OF 2  REGISTRY  COPYRIGHT 2003 ACS on STN
RN   60142-96-3  REGISTRY
CN   Cyclohexaneacetic acid, 1-(aminomethyl)- (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   1-(Aminomethyl)cyclohexaneacetic acid
CN   CI 945
CN   Gabapentin
CN   Go 3450
CN   GOE 2450
CN   GOE 3450
CN   Neurontin
FS   3D CONCORD
MF   C9 H17 N O2
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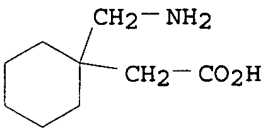
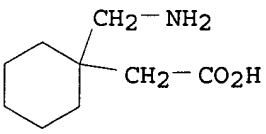
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, PHAR, PHARMASEARCH, PROMT, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

750 REFERENCES IN FILE CA (1907 TO DATE)
29 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
757 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2003 ACS on STN
RN 60142-95-2 REGISTRY
CN Cyclohexaneacetic acid, 1-(aminomethyl)-, hydrochloride (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **Gabapentin hydrochloride**
MF C9 H17 N O2 . Cl H
LC STN Files: CA, CAPLUS, CASREACT, CHEMINFORMRX, CHEMLIST, DRUGPAT, DRUGUPDATES, IFICDB, IFIPAT, IFIUDB, TOXCENTER, USPAT2, USPATFULL
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)
CRN (60142-96-3)



● HCl

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

31 REFERENCES IN FILE CA (1907 TO DATE)
31 REFERENCES IN FILE CAPLUS (1907 TO DATE)

10/024,339

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Delacroix